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Heart failure in Tanzania and Sweden: Comparative characterization and prognosis in the Tanzania Heart Failure (TaHeF) study and the Swedish Heart Failure Registry (SwedeHF)☆

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Abstract

Background—Heart failure (HF) in developing countries is poorly described. We compare characteristics and prognosis of HF in Tanzania vs. Sweden.

Methods—A prospective cohort study was conducted from the Tanzania HF study (TaHeF) and the Swedish HF Registry (SwedeHF). Patients were compared overall (n 427 vs. 51,060) and after

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☆The study conducted at Jakaya Kikwete Cardiac Institute, Muhimbili National Hospital in Dar es Salaam Tanzania and at the Swedish Heart failure registry, in Stockholm Sweden.

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Declaration of interest

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matching 1:3 by gender and age $\pm$ 5 years (n 411 vs. 1232). The association between cohort and all-cause mortality was assessed with multivariable Cox regression.

Results—In the unmatched cohorts, TaHeF (as compared to SwedeHF) patients were younger (median age [inter-quartile range] 55 [40–68] vs. 77 [64–84] years, $p < 0.001$) and more commonly women (51% vs. 40%, $p < 0.001$). The three-year survival was 61% in both cohorts. In the matched cohorts, TaHeF patients had more hypertension (47% vs. 37%, $p < 0.001$), more anemia (57% vs. 9%), more preserved EF, more advanced HF, longer duration of HF, and less use of beta-blockers. Crude mortality was worse in TaHeF (HR 2.25 [95% CI 1.78–2.85], $p < 0.001$), with three-year survival 61% vs. 83%. However, covariate-adjusted risk was similar (HR 1.07, 95% CI 0.69–1.66; $p = 0.760$). In both cohorts, preserved EF was associated with higher mortality in crude but not adjusted analysis.

Conclusions—Compared to in Sweden, HF patients in Tanzania were younger and more commonly female, and after age and gender matching, had more frequent hypertension and anemia, more severe HF despite higher EF, and worse crude but similar adjusted prognosis.

Keywords

Heart failure; Mortality; Tanzania; Sub-Saharan Africa; Sweden

1 Introduction

Heart failure (HF) is emerging as a dominant manifestation of cardiovascular disease in developed countries and rapidly increasing in low-income countries such as those in sub-Saharan Africa (SSA). [1–4] This syndrome has great personal, social and economic implications due to disabling symptoms and high mortality despite standard therapy, if available. [3,4] The clinical characteristics, therapeutic possibilities and prognostic implications of HF have been extensively studied in patients from developed countries but remain largely unexplored in a SSA HF population. [3,5].

In developed countries, HF is in particular prevalent at advanced ages, starting to increase by the age of 60 years, and generally proportionately of similar frequency in gender distribution in some studies [6,7], male predominance in others [8,9] and rarely in women, particularly with preserved ejection fraction (HFpEF) [10]. In the few studies from SSA, the gender distribution appears equal but age is much lower than in developed countries [5,11,12]. Etiologies have historically varied but recent studies suggest that HF in SSA increasingly shifts towards the pattern seen in developed countries with regard to risk factors, etiology and comorbidity [5,7,9,13]. Heart failure therapy has advanced tremendously over the last generation [14] but it remains unclear to what extent this has benefitted patients in SSA.

The aims of the current study were to conduct a patient-level comparison of patients with HF in Tanzania and Sweden, with regard to (1) clinical characteristics and utilization of HF therapy, and (2) prognosis and predictors of prognosis.

2 Methods

2.1 Study design, setting and population

A prospective study was conducted in the Tanzania Heart Failure (TaHeF) and the Swedish Heart Failure Registry (SwedeHF) cohorts. The TaHeF study was initiated at the Jakaya Kikwete Cardiac Institute (JKCI), Dar es Salaam, Tanzania in February 2012 and recruited consecutive patients aged ≥ 18 years with a clinical diagnosis of HF according to the Framingham criteria. Patients were screened (n = 521) and included (n = 427) between 12th February 2012 and 2nd August 2013 in the outpatient clinic and cardiac wards and followed until 30th June 2015. Demographic, social, clinical, comorbidity, laboratory and echocardiographic (general electric vivid 5 with a 2.5–5 MHz probe) variables were obtained as described in detail elsewhere. [5].

SwedeHF provided the study population for comparison with regard to clinical characteristics, therapy, prognosis, and predictors of prognosis. This ongoing nationwide registry was, as previously described, initiated in 2000 [15,16]. Inclusion criteria are clinician-judged HF. The protocol, case report forms and annual reports are available at <http://www.swedehf.se>. Left ventricular ejection fraction (LVEF) is categorized as <30%, 30–39%, 40–49% or ≥ 50%. For the purpose of the present study patients registered from 11th May 2000 to 31st December 2012 and followed until 31st December 2012 were included. Inclusion of SwedeHF patients ended in 2012 because up to that time we had access to socioeconomic and demographic from linked governmental registries. Between 2000 and 2012 in Sweden, there have been no major changes in use of HF medications and only small increases in the use of cardiac resynchronization and implantable cardioverter defibrillator therapy [17]. In Tanzania, HF medications are generally available but devices are not.

2.1.1 Inclusion criteria—A flow chart of patient inclusion is shown in Fig. 1. All eligible patients in TaHeF and SwedeHF were considered except those who a) were lost to follow-up in TaHeF (n = 16); b) those undergoing repeated registration in SwedeHF (n = 29,711); and c) patients in both populations with missing echocardiographic information (n = 18 and 8281, respectively).

2.1.2 Matching—For descriptive characterization and multivariable adjusted analyses, patients were age and gender matched to facilitate age and gender independent comparisons. The TaHeF patients were matched to those in SwedeHF at a ratio of 1 TaHeF to 3 SwedeHF by gender and age (±5 years).

2.2 Selection of variables

Clinically relevant variables collected in TaHeF and in SwedeHF are listed in Table 1. Variables available in both populations were included in the matched analysis and multivariable models and are listed in Table 2.

2.3 Assessment of outcome measure

The index date was defined as date of out-patient visit or date of hospital admission in both TaHeF and SwedeHF. The outcome was time from index date to all-cause mortality. In

TaHeF the patients were followed in the outpatient clinic on a monthly basis. Those who missed their appointments were contacted through mobile phones. Follow-up in clinic and phone contact was sought until June 30, 2015. Patients who were not reached were censored alive at their last confirmed contact. Patients in whom no contact could be established after enrolment were considered lost to follow-up. For patients who died outside of Muhimbili National Hospital the date of death was obtained from a next of kin.

In SwedeHF date of death was obtained from the population registry and patients alive were censored at the time for the last follow-up, December 31st 2012.

2.4 Statistical analyses

Data were entered and validated using OpenClinica software in TaHeF and a web-based case report form (eCRF) into a database managed by the Uppsala Clinical Research Center (UCR, Uppsala, Sweden) in SwedeHF. For baseline description of clinical characteristics, continuous variables were reported as median (interquartile range) and compared using Mann–Whitney U-test while categorical variables were compared by means of the chi-square test. The risk of HF in TaHeF vs. in SwedeHF, overall and by HF with preserved EF (HFpEF; defined as EF $\geq$ 40%) and reduced EF (HFrEF; defined as LVEF $<$ 40%) was assessed in Kaplan–Meier analyses and univariable Cox regressions. Adjustment for clinically relevant confounders was made by multivariable Cox regressions. The interaction between cohort and selected clinically relevant baseline pre-defined sub-groups were assessed in a multivariable Cox regression and displayed in a Forest plot. Furthermore, the association between selected baseline variables and mortality was assessed by multivariable Cox regressions separately in the matched TaHeF and SwedeHF populations. Missing data was handled by multiple imputation ($n = 10$), imputed separately in the SwedeHF and TaHeF populations. Analyses were performed using Stata version 13 statistical package. A two-sided p-value of 0.05 was considered statistically significant.

2.5 Ethical consideration

The establishment of the SwedeHF registry was approved by a multisite Ethics Committee and conforms to the Declaration of Helsinki. Individual patient consent is not required, but the patients are informed of entry into national registries and allowed to opt out. Permission to access the data from the registry for this study was sought from SwedeHF registrar. The TaHeF study was approved by the ethical review board of the Muhimbili University of Health and Allied Sciences (MUHAS). All patients provided written informed consent.

3 Results

3.1 Unmatched cohorts — baseline

Data in the flow chart (Fig. 1) show how patients were selected and analyzed separately as unmatched and matched populations. The age distribution in TaHeF and SwedeHF unmatched ($n = 427$ vs. $51,060$) is shown in Sup-Fig. 1. Baseline characteristics unmatched are shown in Sup-Table 1. 51% of the TaHeF patients were women and median age was 55 years (interquartile range [IQR] 40–68) while a majority of the Swedish patients were men (60%; $p < 0.001$) and median age was 77 (64–84) years ($p < 0.001$). Notable differences

were that TaHeF patients had a lower level of the following; education, LVEF, body mass index (BMI), prevalence of ischemic heart disease, atrial fibrillation, diabetes mellitus and pulmonary disease. The prevalence of hypertension was similar while New York Heart Association (NYHA) classes were more advanced and the prevalence of anemia was higher while the use of beta-blockers was lower in the TaHeF population in which there was no use of revascularization, cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator (ICD).

3.2 Unmatched cohorts — outcomes

Sup-Fig. 2 in the supplement shows survival for the unmatched population. One-year survival rate was 87% in TaHeF vs. 80% in SwedeHF ($p = 0.045$), with a similar 3-year survival rates (61%).

3.3 Matched cohorts — baseline

Four hundred eleven patients in TaHeF were matched by age and gender to 1232 patients in SwedeHF and their baseline characteristics are shown in Table 1. Hypertension and anemia were more prevalent in the TaHeF than in SwedeHF population (47% vs. 37% and 57% vs. 9%, respectively, $p < 0.001$ for both) while the proportion of ischemic heart disease, diabetes and atrial fibrillation were higher in SwedeHF (all, $p < 0.001$). Nitrates, diuretics, spironolactone and digoxin were more commonly used in TaHeF and beta-blockers more frequently in SwedeHF. A comparison of pharmacological therapy in patients with reduced and preserved LVEF is shown in Fig. 2 and Table 1. Overall, HF drug use was greater in SwedeHF but in both populations HF drug therapy was highly used in HFrEF but substantial also in HFpEF.

3.4 Matched cohorts — crude/adjusted mortality and its predictors

Median follow-up in the matched populations was longer in SwedeHF (757 IQR 282–1444 days) than in TaHeF (776 IQR 401–929 days; $p < 0.001$). The crude mortality rate was higher in TaHeF (15/100 person-years) than in SwedeHF (6/100 person-years; Table 2). The one and three year survival rates were 91% (95%CI 90–93%) and 83% (95%CI 80–85%) in SwedeHF vs. 87% (95%CI 83–90%) and 61% (95%CI 54–67%) in TaHeF ($p < 0.001$; Fig. 3a). Survival did not differ between HFpEF vs. HFrEF (TaHeF HFpEF vs. HFrEF $p = 0.550$; SwedeHF HFpEF vs. HFrEF $p = 0.108$). As in the un-matched population survival was worse in TaHeF than SwedeHF both in HFpEF and HFrEF (HFpEF $p < 0.001$; HFrEF $p < 0.001$; Fig. 3b).

The crude and adjusted hazard ratios (HR) for all-cause mortality in TaHeF and SwedeHF are depicted in Table 2. TaHeF patients had a crude HR of 2.25 (95% CI 1.78–2.85; $p < 0.001$). The most pronounced reduction was seen after adjustment for NYHA class and for creatinine clearance, both considerably worse in the TaHeF population. The increased mortality risk for TaHeF patients did not remain after the complete multivariable analysis (HR 1.07, 95% CI 0.69–1.66, $p = 0.760$) (Table 2).

Fig. 4 shows the HR for adjusted mortality in TaHeF vs. SwedeHF (serving as the reference) for clinically relevant pre-specified subgroups of patients with p-values for interaction.

There was no interaction between cohort of recruitment and any of the baseline characteristics except for beta-blocker use, where users had higher risk of death and non-users a trend toward lower risk of death in TaHeF (Fig. 4).

Fig. 5(a–b), shows the association between selected baseline variables and mortality in the matched (a) TaHeF and (b) SwedeHF populations separately. Higher age and NYHA class were associated with increased mortality both cohorts.

4 Discussion

This is the first patient-level comparison of large HF populations with extensive baseline data and rigorous follow-up from a developed country, Sweden, and a SSA country, Tanzania. In an overall un-matched and un-selected population, HF patients in Tanzania were younger, more often female, had lower level of education, more severe HF but less comorbidities except for hypertension and anaemia, and had higher un-adjusted mortality. In a cohort matched by age and gender, patients in Tanzania had more hypertension and anemia, more preserved EF yet more advanced HF of longer duration, and less use of HF medications, and crude mortality was greater whereas covariate adjusted mortality was similar.

4.1 Previous studies

There are few previous studies comparing clinical characteristics and prognosis in HF between developed countries and SSA. Comparison can previously be made only based on separate studies [3,4,13] without direct and matched patient level-comparisons and multivariable adjustments. In the un-matched cohorts, most of the patterns of baseline clinical characteristics, therapy and outcome are consistent with what has been reported and commented in previous unmatched studies/reviews in SSA. [3,5,11,18–20].

4.2 Matched cohorts — baseline characteristics

Heart failure appears to have different characteristics with regard to age and gender in SSA vs. developed countries as previously reported. [11,12,21,22] In the present study, even after matching for these differences, patients in Tanzania had clinically more severe HF by NYHA classification than those in Sweden. This may be attributed to poor and/or later access to care. Even if access to care was adequate in Tanzania, the higher level of education in Sweden may be associated with higher health literacy and propensity to seek care than in Tanzania.

In our matched cohorts where median age was only 55, the high rate of hypertension in the TaHeF as compared to SwedeHF is a public health concern. Several reports from SSA [5,12,20] have emphasized hypertension as an increasingly important contributor to HF. This has also been noted in reports from African American populations [23,24]. These findings may reflect an ethnic characteristic with a genetic predisposition which may be exacerbated by hypertension more frequently leading to organ-related complications at an earlier stage than in Europeans [3,5,19]. Such risk may explain the considerably worse renal function in TaHeF patients in the current study.

With regard to comorbidities, anemia, a strong predictor of mortality and morbidity in HF [5,19,25], also appeared to be highly prevalent in TaHeF, possibly explained by renal dysfunction and severity of HF, although these alone do not seem to explain the large discrepancy [25].

In contrast, other comorbidities such as diabetes, ischemic heart disease and atrial fibrillation were less common in TaHeF, and presently reflect risk factors and disease patterns dominating in developed countries but increasing also in developing countries. The distribution of HFpEF (where atrial fibrillation is more common) vs. HFrEF weighed toward more HFpEF in TaHeF, consistent with less ischemic heart disease and more hypertension as plausible underlying etiologies.

Fundamental HF therapy in the form of renin–angiotensin system (RAS) inhibition (ACE-inhibitors or angiotensin receptor blockers) was highly utilized in both TaHeF and SwedeHF, and spironolactone was used to an even greater extent in TaHeF. In fact, given the worse renal function in TaHeF (median creatinine clearance 69 ml/min in this young population), the use of RAS-antagonists and mineralocorticoid receptor antagonists was notably high. In contrast, the low use of beta-blockers in TaHeF is concerning, and may reflect fear of worsening HF in patients with already advanced syndrome (higher NYHA class). Digoxin and nitrates are readily available drugs historically used extensively in HF, and their greater use in TaHeF may reflect slower adoption of contemporary HF management and/or lower cost of these drugs.

Despite a 16% prevalence of atrial fibrillation in TaHeF the use of oral anticoagulants was nearly non-existent, which is concerning with arrhythmia already identified as an important risk marker of poor prognosis in HF in Tanzania [5]. With limited access to blood sampling for adjustment of warfarin-based anticoagulation and newer oral anti-coagulants remaining patented and expensive, atrial fibrillation may indeed emerge as an important public health problem in SSA countries, whether in the presence or absence of HF.

At the time of this study coronary revascularization was not performed in Tanzania and therefore only available for patients able to travel and be treated abroad. As SSA countries increasingly resemble developed countries with regard to lifestyle and risk factors, acute coronary syndromes may soon contribute to morbidity and mortality as well as the incidence and severity of HF. Similarly, implantable devices for cardiac resynchronization and/or cardioversion–defibrillation were not available to TaHeF patients.

Despite a lack of efficacy evidence there was considerable use of most HF drugs also in HFpEF in both TaHeF and SwedeHF. This may reflect the use of these drugs for hypertension or a perception that they may be effective in HFpEF.

4.3 Matched cohorts — all-cause mortality and its predictors

After age and gender matching, TaHeF patients had more than twice the crude risk of death compared to those in SwedeHF. As this greatly reflected more severe NYHA class and impaired renal function, and to some extent lower use of some evidence based HF drugs, there was no significant difference in risk after multivariable adjustment. The few previous

studies comparing HF in SSA vs. developed countries did not match the patients or perform adjustments for important confounders [3,5,13]. Our findings suggest that previous data reflect a combination of younger age but greater severity of HF and less well developed treatment in SSA countries, with opposite and cancelling effects on outcomes. Our matched and carefully adjusted analyses suggest that there is nothing intrinsic about patients or health care systems in lower income countries that necessarily portends worse prognosis, but that the more severe (unadjusted) prognosis can be accounted for by later access to care and a thereby more advanced HF at the first presentation in addition to less use of some proven HF therapy, conditions which can be remedied.

Previous observations of similar prognosis in HFpEF and HFrEF [26,27] were echoed in our study, the first comparison of HFpEF vs. HFrEF in SSA vs. developed countries. Other studies, in particular clinical trials, have shown lower mortality in HFpEF populations [28,29].

In interaction analyses, TaHeF origin was associated with significantly greater mortality in beta-blocker treated patients. With multiple subgroup tests, this could be due to chance or may reflect the greater NYHA severity in TaHeF, where rapid initiation and up-titration in patients with limited follow-up and access to care may conceivably be associated with harm.

4.4 Strengths and limitations

The present findings are strengthened by direct matched populations, with individual patients pooled in the same statistical model, and thus reducing the risk of biased comparisons and allowing for adjustment of a number of cofounders. However, TaHeF was performed in a single specialized clinic, which may not be as generalizable as the nationwide SwedeHF registry. However JKCI is a national referral hospital receiving patients from all over Tanzania. The SwedeHF and TaHeF cohorts were from different enrolment years, but treatment has not changed notably in the 2000s, even in SwedeHF [17]. Nonetheless, additional studies comprising more care settings and countries representing SSA and developed countries will be needed to generalize the results.

5 Conclusions

In this first large comprehensive patient-level comparison of patients with HF in a developed country versus a SSA country, patients in SSA were younger and more commonly female. After age and gender matching, SSA patients had more frequent hypertension and anemia and less use of HF medications, and more severe HF despite higher EF and worse crude but similar adjusted prognosis. By improving detection and treatment of hypertension and anemia as well as more use of evidence-based HF medications, prognosis in patients with HF in SSA may be improved.

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Fig. 1.

Flow chart for patients included in TaHeF and SwedeHF populations. Legend: * Matching using <http://www.mayo.edu/research/documents/gmatchsas/doc-10027248> Mayo Clinic <http://www.mayo.edu/research/departments-divisions/departments-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros>

Fig. 2.
Medication use in TaHeF and SwedeHF matched populations according to pEF vs. rEF.

Fig. 3.
Kaplan-Meier curves in the TaHeF and SwedeHF matched populations (a) overall survival, (b) survival according to pEF vs. rEF.

Fig. 4.

Adjusted hazard ratio (95% CI) for mortality in TaHeF vs. SwedeHF (reference group) for matched populations in selected subgroups.

Fig. 5. Association between selected baseline variables and mortality in the matched TaHeF (5a) and SwedeHF (5b) populations separately.

Table 1Baseline characteristics in the matched population^a.

	<u>TaHeF</u>			<u>SwedeHF</u>			
	<u>n = 411</u>			<u>n = 1232</u>			
	<u>Missing</u>			<u>Missing</u>			p-Value
	%	n	% or IQR	%	n	% or IQR	
<i>Demographics</i>							
Age ^b	–	55	41–67	–	55	41–67	
Gender (male) ^b	–	204	50	–	612	50	
Ever smoked (%)	–	56	14	17	595	58	<0.001
Education level	–			1.1			
None		84	20		0	0	<0.001
Basic		165	40		429	35	<0.001
Secondary school		94	23		538	44	<0.001
University		68	17		251	21	<0.001
Caregiver unit	–			–			
Inpatient		111	27		581	47	<0.001
Outpatient		300	73		651	53	<0.001
Duration of HF	–			0.4			
<6 months		136	33		749	61	<0.001
6 months		275	67		478	39	<0.001
NYHA class	–			21			
I–II		83	20		661	68	<0.001
III–IV		328	80		308	32	<0.001
<i>Medical history</i>							
Ischemic heart disease	–	40	10	4.4	348	30	<0.001
Dilated cardiomyopathy	–	95	23	2.9	327	27	0.104
Hypertension	–	194	47	2.4	441	37	<0.001
Atrial fibrillation	–	67	16	0.2	378	31	<0.001
Pulmonary disease	–	13	3	2.8	158	13	<0.001
Diabetes	–	49	12	0.6	256	21	<0.001
Calcific valve disease	–	3	1	2.1	212	18	<0.001
<i>Treatment</i>							
Valve intervention	8.3	1	0	1.4	69	6	<0.001
ACE inhibitor	–	279	68	0.4	901	73	0.031
ARB	–	111	27	2.1	249	21	0.009
RAS (ACEi and/or ARB)	–	378	92	0.2	1110	90	0.376
Aldosterone antagonists	–	297	72	0.7	357	29	<0.001
Betablockers	–	145	35	0.4	1088	89	<0.001
Diuretics	–	355	86	0.6	811	66	<0.001
Digoxin	–	159	39	0.4	187	15	<0.001

	<u>TaHeF</u>			<u>SwedeHF</u>			
	<u>n = 411</u>			<u>n = 1232</u>			
	<u>Missing</u>			<u>Missing</u>			p-Value
	%	n	% or IQR	%	n	% or IQR	
Oral anticoagulants	–	11	3	0.3	406	33	<0.001
Atrial fibrillation = yes		1	1.5		255	68	<0.001
Platelet inhibitors	–	113	27	0.5	458	37	<0.001
Ischemic heart disease = yes		25	63		268	77	<0.052
<i>Clinical</i>							
Blood pressure	–						
Systolic		126	110–150	0.5	120	109–135	<0.001
Diastolic		80	72–96	0.9	73	65–80	<0.001
Heart rate	–	88	72–104	5.9	72	63–82	<0.001
Body mass index	–	24.7	22–28	48	27.2	23.6–31.1	<0.001
<20		67	16		63	10	<0.001
20–25		180	44		203	32	<0.001
26–30		85	21		182	29	<0.001
>30		75	18		187	29	<0.001
<i>Echocardiography/laboratory/chest X-ray</i>							
LVEF (%)	8.3			–			
<30		70	19		449	36	<0.001
30–39		96	25		335	27	<0.001
40–49		140	37		236	19	<0.001
50		71	19		212	17	<0.001
40		211	56		448	36	<0.001
<40		166	44		784	64	<0.001
ACE inhibitor		119	71	0.5	16,808	71	1.000
ARB		41	24	1.8	4961	21	0.343
RAS							
Beta blockers		74	44	0.5	21,288	90	<0.001
Aldosterone antagonist		125	47	8.1	7667	32	<0.001
Potassium (mmol/L)	4.6	4.1	3.7–4.6	34.3	4.1	3.8–4.4	0.345
Creatinine clearance (mL/min)	4.6	69	49–91	8.2	93	67–123	<0.001
Hemoglobin (g/L)	6.3	119	106–132	0	136	124–148	<0.001
Anemia		218	57	0	108	9	<0.001
Pulmonary congestion	–	121	29	43	285	40	<0.001
Cardiomegaly on X-ray	–	357	87	43	331	47	<0.001

Notes

^aContinuous variables are presented as median and lower and upper quartiles (Q1; Q3) and categorical variables as numbers (n) and percentages when not otherwise stated). Abbreviations: IQR, interquartile range; ACEi, angiotensin converting enzyme inhibitor; angiotensin receptor blocker; RAS, renin–angiotensin system; LVEF, left ventricular ejection fraction.

^bVariables used for matching.

Table 2

Crude and adjusted risk of mortality in TaHeF vs. SwedeHF.

Events/person-years	TaHeF vs. SwedeHF*	
	15/1000 vs. 6/1000	
	Hazard ratio (95%CI)	p-Value
Crude mortality	2.25 (1.78–2.85)	<0.001
Multivariable model**	1.07 (0.69–1.66)	0.760
NYHA class (2 categories [‡])	1.51 (1.17–1.95)	0.001
LVEF (4 categories [‡])	2.17 (1.71–2.77)	<0.001
Caregiver unit (2 categories [‡])	2.64 (2.07–3.37)	<0.001
All 3 above (NYHA/LVEF/caregiver)	1.56 (1.17–2.06)	0.002
Educational level	1.96 (1.52–2.52)	<0.001
Duration of HF	1.95 (1.53–2.48)	<0.001
Ischaemic heart disease	2.69 (2.10–3.44)	<0.001
Hypertension	2.22 (1.75–2.81)	<0.001
Atrial fibrillation/flutter	2.71 (2.13–3.46)	<0.001
RAS	2.28 (1.80–2.88)	<0.001
Betablockers	2.02 (1.52–2.69)	<0.001
Aldosterone antagonist	1.93 (1.49–2.49)	<0.001
All 3 above (RAS/BB/Aldo)	1.78 (1.32–2.41)	<0.001
Heart rate	1.98 (1.53–2.55)	<0.001
Systolic blood pressure	2.31 (1.82–2.94)	<0.001
Body mass index (continuous, using restricted cubic splines)	2.06 (1.62–2.63)	<0.001
Creatinine clearance (continuous, using restricted cubic splines)	1.45 (1.14–1.85)	0.003
NYHA + creatinine clearance	1.08 (0.83–1.39)	0.585

* Reference category;

** model was adjusted for NYHA, LVEF, HF duration, in/out-patient, education, smoking, creatinine clearance, systolic blood pressure, heart rate, body mass index, ischemic heart disease, atrial fib/flutter, hypertension, anemia, diabetes, lung disease, calcific valve disease, RAS, betablockers, aldosterone antagonist, digoxin, diuretics = 22 variables; CI = confidence interval ;

[‡]categories according to Table 1.