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RESEARCH ARTICLE

Combination of heart failure and atrial fibrillation worsens ethnicity-related disparity: an individual patient-level meta-analysis of randomized trials

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Abstract

Aims

Ethnicity can influence patient outcomes and treatment efficacy, but knowledge is limited on how multimorbidity interacts with clinical events, for example when heart failure (HF) and atrial fibrillation (AF) combine.

Methods and Results

16 713 patients were included from 12 randomized placebo-controlled trials in HF (11 vs beta-blockers and 1 vs spironolactone), of which 13 568 patients (81.2%) were in sinus rhythm and 3145 (18.8%) had comorbid AF at baseline. Non-white ethnicity was recorded in 1899 (11%), with these patients being younger than those of white ethnicity (median age 58 vs 67 years), higher rates of diabetes and hypertension, and lower left-ventricular ejection fraction (median 25% vs 30%). During median follow-up of 1.4 years (interquartile range 0.8–2.3), the primary outcome of all-cause mortality occurred in 394 (21%) non-white patients and 2142 (15%) white patients, with confounder-adjusted hazard ratio (HR) 1.36, 95% CI 1.20–1.54; $P < .001$. The impact of ethnicity on death was greater in patients with coexisting HF and AF (non-white vs white HR 2.05; 95% CI 1.55–2.70; $P < .001$) than in those with HF in sinus rhythm (HR 1.24; 95% CI 1.08–1.41; $P = .002$). The interaction *P*-value was .003, and confirmed using propensity-score matching to account for baseline differences ($P = .009$). Similar disparities with ethnicity were seen for the secondary outcomes of cardiovascular and HF-related death, and cardiovascular and HF-related hospitalization.

Conclusion

Non-white patients with HF and reduced ejection fraction suffer from substantially higher rates of death than white patients, with comorbid atrial fibrillation leading to significant worsening of this ethnicity-related disparity.

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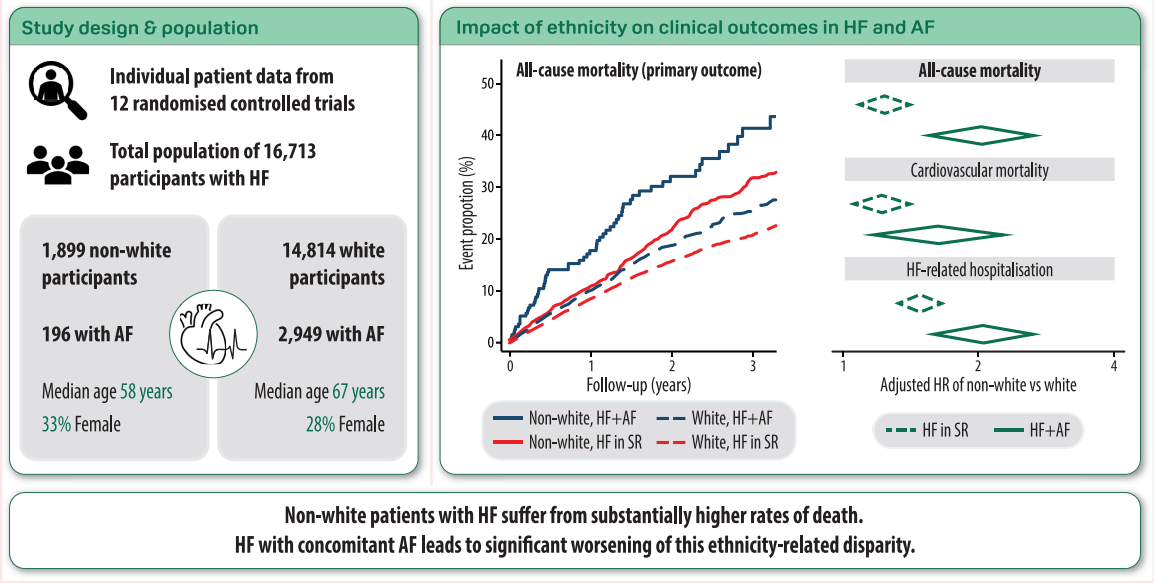
Graphical abstract



Analysis of individual patient data from heart failure trials indicates an ethnic disparity in clinical outcomes, which is exacerbated by cardiovascular multimorbidity. AF, atrial fibrillation; HF, heart failure; HR, hazard ratio; SR, sinus rhythm.

Keywords Ethnicity • Heart failure • Atrial fibrillation • Mortality • Hospitalization

Introduction

Heart failure (HF) and atrial fibrillation (AF) are two emerging public health concerns due to rapid increases in prevalence and their association with substantial morbidity and mortality. The conditions frequently coexist,[1] and patients with concomitant HF and AF may not respond to conventional guideline-recommended therapy leading to even higher rates of adverse outcomes.[2,3] On a background of numerous patient-specific factors, ethnicity has long been considered an important contributor to variation in prognosis and treatment efficacy.[4] The term ethnicity encompasses biological parameters and cultural attributes, with health perception, health behaviour and healthcare access all contributing to differences in clinical outcomes.[5] These factors affect how patients present, the treatments they receive and their follow-up, making direct ethnicity comparisons challenging. Knowledge on the true impact of these issues on prognosis in patients with either HF or AF is available but limited.[6,7] In contrast, there is no consistent information on ethnicity in patients that have both HF and AF, with two observational studies finding conflicting results.[8,9]

This study was designed to examine if the impact of ethnicity on clinical events is compounded by multimorbidity. The null hypothesis tested was of no difference in death [and other cardiovascular (CV) events] between non-white and white patients when comparing HF in sinus rhythm and HF with concomitant AF. Individual patient-level data from randomized controlled trials (RCTs) were utilized to reduce bias related to differences in definitions, healthcare delivery and outcome ascertainment that are commonly encountered in observational research.

Methods

Ethics

The study complies with the Declaration of Helsinki and the research proposal was approved by the University of Birmingham Ethical Review Committee (ERN_20-0647).

Study selection and data harmonization

Anonymized individual patient data were obtained from 12 RCTs comprising patients with HF, with or without concomitant AF (Supplementary Figure S1). All trials had appropriate ethical approvals, and a low risk of bias evaluated using the Cochrane Collaborations Risk of Bias Tool (Supplementary Figure S2). Trial data were obtained from the Beta Blockers in Heart Failure Collaborative Group (BB-meta-HF; Clinicaltrials.gov NCT0083244[10]) and the National Heart, Lung and Blood Institute Biologic Specimen and Data Repositories Information Coordinating Centre (BioLINCC).[11,12] A process of data harmonization and data quality assessment was undertaken to combine all trial datasets using an established and robust approach.[2,13]

Population

The combined population from the 12 RCTs was divided into two groups according to cardiac rhythm status (sinus rhythm or AF) determined on the baseline electrocardiogram. Atrial flutter was not always indicted separately and so was included in the AF group, and those with a missing ECG or paced rhythm were excluded. Coding for each participant's ethnicity was accepted from each corresponding trial database, and participants with missing ethnicity excluded. The categories of ethnicity were then collapsed into non-white and white groups. To avoid introducing bias for data not missing at random, no data imputation methods were used.

Outcomes

The primary outcome for this study was all-cause mortality.

Secondary outcomes were CV-related mortality, HF-related mortality, CV-related hospitalization and HF-related hospitalization. Each trial performed independent adjudication of clinical outcomes.

Statistical analysis

Baseline data were summarized with mean and standard deviation, median and interquartile range (IQR), or frequency and percentage. Differences between groups were analysed using a *t*-test, Mann–Whitney *U* test, or χ^2 test.

Table 1 Baseline demographics by ethnicity

Baseline characteristic	Non-white ($n = 1899$)	White ($n = 14\,814$)	*P*-value
Intervention arm, *n* (%)	986 (51.9%)	7510 (50.7%)	.31
Heart rhythm			
Sinus rhythm, *n* (%)	1703 (89.7%)	11 865 (80.1%)	<.001
Atrial fibrillation, *n* (%)	196 (10.3%)	2949 (19.9%)	<.001
Female gender, *n* (%)	634 (33.3%)	4089 (27.6%)	<.001
Age, median years (IQR)	58.0 (49.0–67.0)	67.0 (58.0–73.7)	<.001
BMI, median kg/m^2 (IQR)	28.0 (24.2–32.9)	27.1 (24.4–30.6)	<.001
Systolic BP, median mmHg (IQR)	120 (108–134)	125 (112–140)	<.001
Diastolic BP, median mmHg (IQR)	75 (68–82)	77 (70–82)	<.001
Heart rate, mean (SD)	82.0 (13.8)	79.1 (12.8)	<.001
LVEF, median (IQR)	0.25 (0.19–0.34)	0.30 (0.22–0.38)	<.001
NYHA class III/IV, *n* (%)	1362 (72.1%)	8039 (54.5%)	<.001
Comorbidities			
Previous myocardial infarction, *n* (%)	662 (34.9%)	7905 (53.4%)	<.001
Previous stroke, *n* (%)	73 (7.1%)	693 (6.6%)	.56
Previous CABG or PCI, *n* (%)	342 (18.1%)	3202 (22.2%)	<.001
Hypertension, *n* (%)	1314 (70.5%)	7697 (53.2%)	<.001
Peripheral arterial disease, *n* (%)	156 (8.6%)	1180 (8.3%)	.73
Diabetes mellitus, *n* (%)	747 (40.3%)	3755 (25.9%)	<.001
Medications			
Diuretic, *n* (%)	1509 (93.7%)	10 387 (82.7%)	<.001
ACE inhibitor or ARB, *n* (%)	1543 (95.8%)	11 874 (94.5%)	.036
Aldosterone antagonist, *n* (%)	67 (4.7%)	1243 (8.6%)	<.001
Calcium channel blocker, *n* (%)	202 (10.9%)	1630 (11.2%)	.66
Statin, *n* (%)	451 (24.8%)	3625 (25.6%)	.44
Digoxin, *n* (%)	1346 (72.2%)	7221 (49.9%)	<.001
Oral anticoagulant, *n* (%)	660 (35.4%)	4592 (31.7%)	.002

IQR, interquartile range; BMI, body mass index; BP, blood pressure; SD, standard deviation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Failure Association; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Refer to Supplementary Table S2 and S3 for missing data.

Incidence rates per 1000 person-days and incidence rate ratios were used to compare outcomes by ethnicity. Time-to-event analyses using Cox proportional hazard ratio (HR) models was the primary analysis, with proportionality testing used to confirm the hazards were proportional over time. Regression models included adjustment for age, gender, New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), previous myocardial infarction (MI), diabetes and hypertension. Two interactions were found to be significant and included in the model: age and LVEF, and LVEF and NYHA class. To account for observed baseline differences between the ethnicity groups, a propensity-matched analysis was performed as a sensitivity analysis. The propensity-matched model employed one-to-one nearest neighbour matching with replacement.[14] This generated an average treatment effect on the treated, summarizing the difference in probabilities of an event occurrence between non-white patients and their propensity-matched white counterparts. Odds ratios were obtained by performing a logistic regression on the propensity-score matched groups. An exploratory analysis of treatment efficacy stratified by ethnicity was also performed, but only where randomized treatment effects were significant (within each rhythm group). This was done using an intention-to-treat approach according to the randomized allocation, regardless of treatment discontinuation or cross-over. All statistical analyses were performed using Stata (version 17, StataCorp LP, Texas) and a two-tailed *P*-value of <.05 was used to denote statistical significance.

Results

The study included 12 RCTs of participants with HF (Supplementary Figure S1), including 10 trials with predominantly reduced LVEF (<40%),[12,15–23] 1 trial with a range of LVEF,[24] and 1 trial with LVEF ≥45%.[11] Overall, the patient sample represented HF with severely reduced ejection fraction, with a median LVEF of 30% (IQR 22%–37%). Individual patient data from 16 713 participants with HF were analysed, of which 13 568 (81.2%) were in sinus rhythm at baseline and 3145 (18.8%) in AF. Non-white ethnicity was recorded in 1899 (11%) and white in 14 817 (89%) (Supplementary Table S1 for breakdown of ethnicity by rhythm status). There were significant differences across baseline characteristics between non-white and white patients (*Table 1*; Supplementary Tables S2 and S3 for demographics by rhythm status). The non-white cohort was younger, with median age 58.0 years (IQR 49.0–67.0) vs 67.0 years for the white group (IQR 58.0–73.7; $P < .001$). Non-white participants had a lower rate of prior MI, more hypertension and diabetes, lower median LVEF [25% (IQR 19%-34%) vs 30% for white participants (IQR 22%–38%)], and were typically more symptomatic (NYHA class III/IV 72.1% vs 54.3%). There was no difference in the allocation to intervention or placebo with regards to ethnicity ($P = .31$). For the propensity-matched analyses, the average

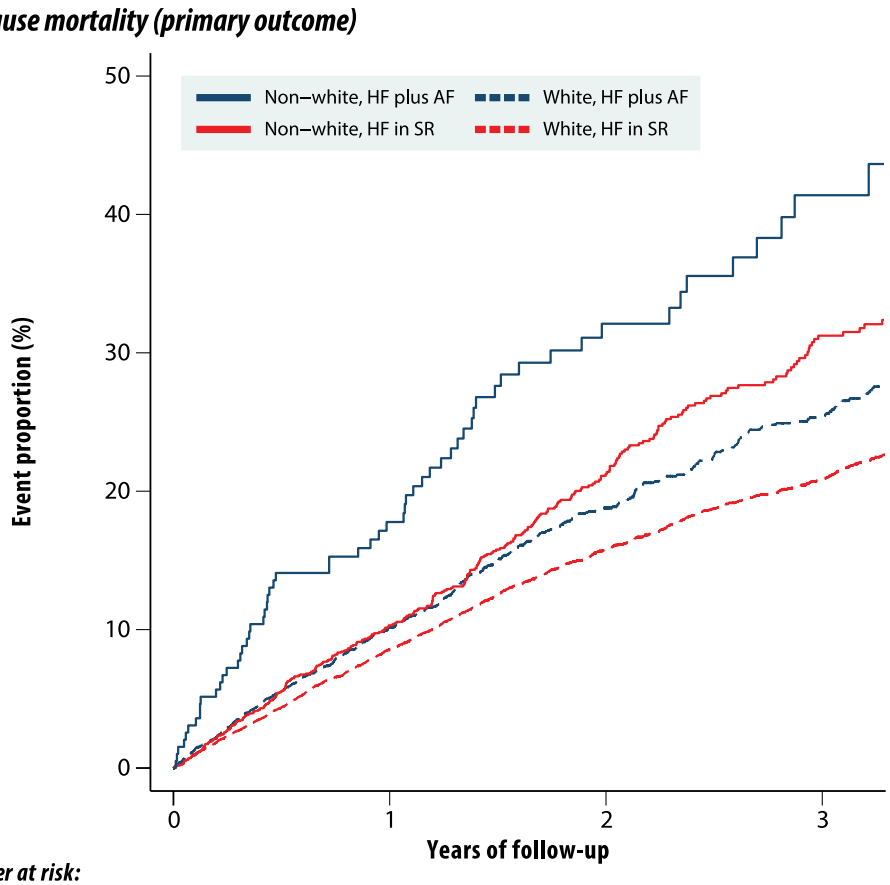


Figure 1 Kaplan–Meier curves for all-cause mortality stratified by ethnicity. Comparing trial participants with heart failure in sinus rhythm and heart failure plus AF. AF, atrial fibrillation; HF, heart failure; SR, sinus rhythm

treatment effect on the treated was estimated in 1354 non-white patients and 1011 white patients after baseline characteristics were balanced across groups ($P > .05$ for all included covariates; Supplementary Table S4).

Primary outcome: all-cause mortality

During median follow-up of 1.4 years (IQR 0.8–2.3), death occurred in 394 (20.7%) non-white patients and 2142 (14.5%) white patients. The adjusted HR of all-cause mortality for non-white vs white was 1.36, 95% CI 1.20–1.54; $P < .001$. When stratified according to rhythm status, non-white HF patients with concomitant AF had the highest rate of all-cause mortality (*Figure 1*). The non-white vs white adjusted HR for all-cause mortality in patients with HF in sinus rhythm was 1.24 (95% CI 1.08–1.41; $P = .002$) and 2.05 for those with HF plus AF (95% CI 1.55–2.70, $P < .001$); *Table 2*. The differential impact of ethnicity was significantly greater with HF and AF combined (interaction $P = .003$). Results were confirmed in the propensity score-matched analysis ($P = .12$ for HF in sinus rhythm; $P = .001$ for HF plus AF; P for comparison = .009; Supplementary Table S5).

Secondary outcomes

Incidence rates of CV and HF-related death, CV-hospitalization, and HF-hospitalization were significantly higher in non-white vs white participants (*Table 2*), persisting after multivariate adjustment for all secondary outcomes apart from HF mortality (*Figure 2*). Point estimates were consistently greater for patients with combined HF plus AF compared with HF in sinus rhythm, but interactions were not significant for any secondary outcome after adjustment (*Table 2*) or using propensity score matching (Supplementary Table S5).

Exploratory analysis of therapeutic efficacy

Treatment effects were not significant for beta-blockers vs placebo in HF plus AF, or for spironolactone vs placebo in HF with sinus rhythm or AF (Supplementary Table S6). Analysis of beta-blockers for HF in sinus rhythm demonstrated significantly lower all-cause mortality vs placebo for white patients (HR 0.70, 95% CI 0.63–0.78; $P < .001$), which was not seen in the non-white group (HR 1.00; 95% CI 0.79–1.27; $P = .99$); P-interaction for ethnicity = .008 and propensity-matched

Table 2 Primary and secondary outcomes

Non-white vs white	Crude event numbers (%)	Incidence rate ratio (95% CI), *P*-value	Adjusted hazard ratio (95% CI), *P*-value	Interaction *P*-value for additional comorbidity
All-cause mortality				
HF in sinus rhythm	330/1703 (19.4%) vs 1610/11 865 (13.6%)	1.40 (1.23–1.58), *P* < .001	1.24 (1.08–1.41), *P* = .002	0.003
HF plus AF	64/196 (32.7%) vs 532/2949 (18.0%)	1.85 (1.39–2.42), *P* < .001	2.05 (1.55–2.70), *P* < .001	
Cardiovascular-related mortality				
HF in sinus rhythm	278/1703 (16.3%) vs 1317/11 865 (11.1%)	1.42 (1.24–1.63), *P* < .001	1.22 (1.05–1.41), *P* = .007	0.14
HF plus AF	45/196 (23.0%) vs 432/2949 (14.6%)	1.54 (1.09–2.21), *P* = .012	1.63 (1.17–2.27), *P* = .004	
Heart failure-related mortality				
HF in sinus rhythm	75/1703 (4.4%) vs 376/11 865 (3.2%)	1.38 (1.06–1.77), *P* = .016	1.16 (0.89–1.52), *P* = .28	0.24
HF plus AF	15/196 (7.7%) vs 153/2949 (5.2%)	1.48 (0.79–2.56), *P* = .17	1.72 (0.98–3.01), *P* = .06	
Cardiovascular-related hospitalization				
HF in sinus rhythm	557/1703 (32.7%) vs 2962/11 865 (25.0%)	1.29 (1.18–1.42), *P* < .001	1.28 (1.16–1.42), *P* < .001	0.14
HF plus AF	79/196 (40.3%) vs 879/2949 (29.8%)	1.61 (1.26–2.03), *P* < .001	1.56 (1.23–1.98), *P* < .001	
Heart failure-related hospitalization				
HF in sinus rhythm	470/1703 (27.6%) vs 1736/11 865 (14.6%)	1.94 (1.75–2.15), *P* < .001	1.49 (1.33–1.66), *P* < .001	0.07
HF plus AF	69/196 (35.2%) vs 606/2949 (20.5%)	2.07 (1.59–2.66), *P* < .001	2.05 (1.59–2.65), *P* < .001	

HF, heart failure; AF, atrial fibrillation; CI, confidence interval.

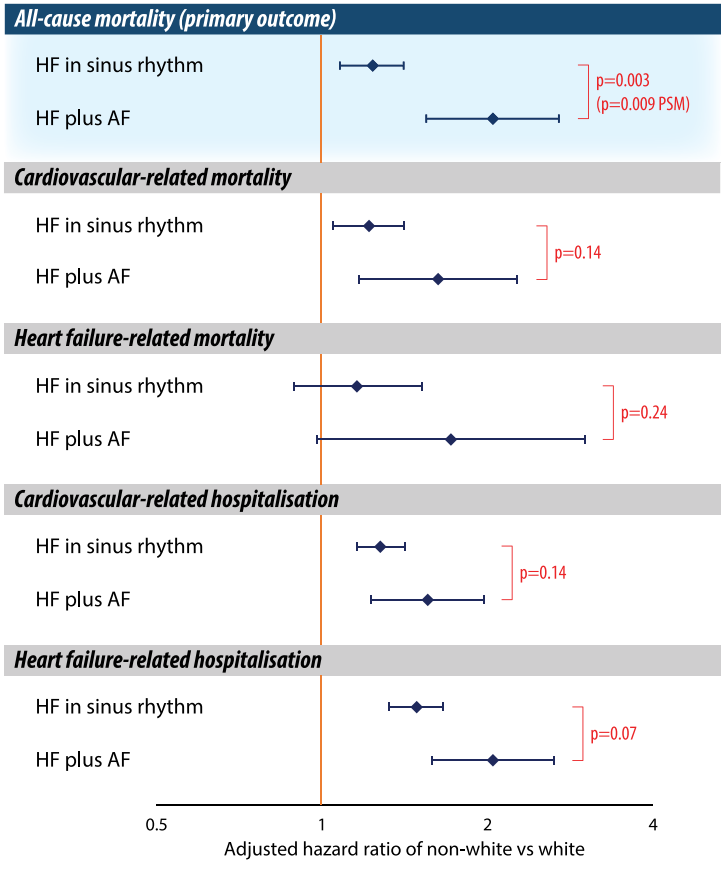


Figure 2 Forest plot of mortality and hospitalization outcomes in white and non-white patients according to AF status. Adjusted hazard ratios with 95% confidence intervals and interaction *P*-values. Cox-proportional hazards models were adjusted for age, gender, left ventricular ejection fraction, New York Heart Association class, previous myocardial infarction, diabetes, and hypertension. AF, atrial fibrillation; HF, heart failure; PSM, propensity-score matched analysis

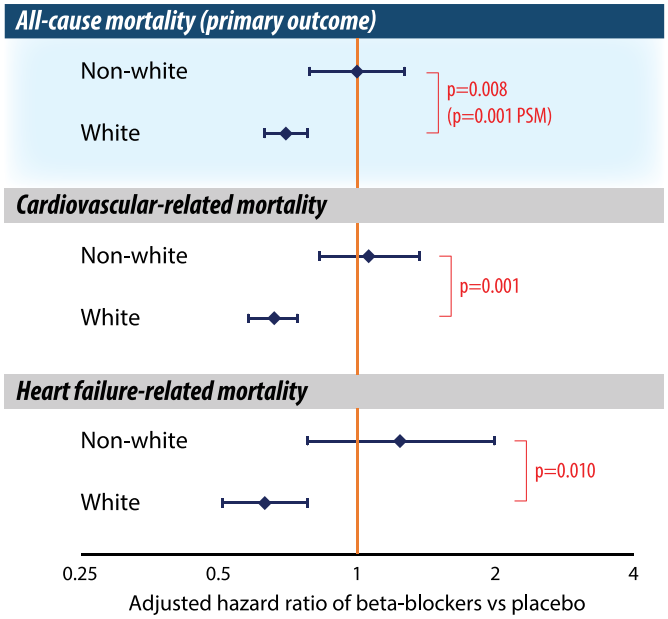


Figure 3 Exploratory analysis of mortality in white and non-white patients according to beta-blocker use in sinus rhythm. Adjusted hazard ratios with 95% confidence intervals and interaction *P*-values. Cox-proportional hazards models adjusted for age, gender, left ventricular ejection fraction, New York Heart Association class, previous myocardial infarction, diabetes, and hypertension. PSM, propensity-score matched analysis

interaction $P = .001$ (*Figure 3* and Supplementary Table S7). The significant differential impact of beta-blockers vs placebo according to ethnicity was also seen for CV-related and HF-related mortality (*Figure 3* and Supplementary Table S7).

Discussion

Using individual patient data from RCTs, this study found that the combination of HF with reduced LVEF and AF worsens the disparity in all-cause mortality seen between non-white and white patients. There was a quarter increase in hazard for non-white patients with HF alone, vs a two-fold increase in hazard compared with white patients for those with HF plus AF. The incidence of the secondary outcomes CV-related death, HF-related death, CV-related hospitalization, and HF-related hospitalization were also significantly higher in non-white patients.

Ethnicity plays a major and complex role in healthcare, impacting on presentation, diagnosis, treatment, and outcomes. It is also closely related to a range of confounding factors that interrupt any direct association with reported CV events and death. For example, individuals in different ethnic groups can present later with their initial symptoms, may be less likely to seek healthcare assistance, or face barriers to access healthcare.[25] Previous observational studies have suggested that non-white patients are significantly less likely to be discharged on appropriate medical therapy,[8] or receive interventional procedures such as cardiac resynchronization therapy for HF and catheter ablation for AF.[9,26] All of these factors (and more) will contribute to the worse prognosis seen in non-white patients. The concept that a combination of health conditions could exacerbate health inequality has been demonstrated beyond cardiology. In both the USA and UK, studies have shown the mortality rate associated with multimorbidity is higher in certain ethnic groups compared with white patients.[27]

To counter some of the biases of observational data, this study only included randomized trials, with double-blinding, intention-to-treat analysis and independent adjudication of outcome events. Further, the use of individual patient-level data allowed for adjustment and matching with time-to-event analyses. However, none of the trials were randomized on the basis of ethnicity, so residual confounding for the aforementioned confounders will still apply and we clearly demonstrated a more severe HF phenotype at baseline in non-white participants. Propensity-matched analysis is not a surrogate for randomization, and the more limited matched sample size may not be powered to detect interaction by ethnicity. The exploratory analysis of treatment effect by ethnicity was only possible for beta-blockers in patients with HF in sinus rhythm, as there was no significant benefit for beta-blockers vs placebo in HF plus AF,[2,3] or spironolactone vs placebo in any group.[11] Other HF treatments were not included in the two trial databases used to obtain individual patient-level data. In direct contrast to the white participants, non-white patients appeared to lack benefit from beta-blockers, although this may have been related to later presentation as evidenced by lower LVEF, more symptoms and greater need for diuretics. We found no difference in randomization to the intervention groups related to ethnicity, although there were differences in other medical therapy, notably less aldosterone antagonists in the non-white participants. Unlike prior observational studies, the non-white group in these RCTs had higher levels of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker and oral anticoagulation prescription. An additional factor in treatment response that we could not assess were genetic polymorphisms that can affect beta-blocker response,[28] and have different prevalence across ethnic groups.[29] There are also numerous differences related to ethnicity in the pharmacokinetic and pharmacodynamic response to many other CV therapies.[30]

This study was limited by the numbers of non-white participants in these trials, requiring a combined assessment of non-white vs white groups. It was not possible to analyse outcomes for individual ethnicities, and by amalgamating these groups into a single cohort, we may have obscured important variations in outcome rates between different

non-white ethnicities. Socioeconomic status, and related factors such as nutrition and salt intake, are other important confounders with ethnicity, but information on these variables was not collected in the component trials. The study inclusion criteria did not select on the basis of LVEF as there are known biases in LVEF assessment between ethnic groups. However, by nature of the trials included the findings from this study only apply to HF with reduced ejection fraction, with additional work warranted to explore if these results also apply to HF with preserved LVEF. Further, the trials incorporated are historical landmark studies conducted before routine use of additional treatments such as cardiac resynchronization therapy, neprilysin inhibition, and sodium-glucose cotransporter-2 inhibitors, and before widespread uptake of interventional AF therapies such as catheter ablation. However, the newer HF therapies are based on the foundation of ACEi, beta-blockers and aldosterone antagonists which were the subject of the included trials. These trials also had a lower proportion of patients with AF than expected from current clinical practice (where awareness and detection of AF have improved), which limited our power to confirm significant differences for comorbidity across the secondary outcomes. Extrapolation of the study findings to recent therapies and real-world data sources is a suggested next step to confirm the extent of ethnic disparities in the care of patients with HF.

The results of this study should spur action to improve research and the management of HF across all ethnic groups. Concerted effort is needed to address the under-representation of ethnic minorities in medical research. A broader awareness of prescription and therapeutic biases in routine practice is critical. Deeper focus is required by all healthcare practitioners of the individual issues that each patient may face in order to achieve optimal outcomes, reduce mortality and morbidity, and reduce the substantial healthcare and social costs of HF.

Conclusion

Analysis of patient-level data from double-blind, historical randomized trials demonstrated a substantial excess of mortality for non-white patients with HF and reduced LVEF, compared with those of white ethnicity. The divergence in clinical outcomes was exacerbated in patients with additional AF, which is one of the most common concomitant conditions in HF. Further research is urgently needed to understand if different non-white groups have varying levels of risk and treatment efficacy.

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Supplementary data

Supplementary data are available at *European Journal of Heart Failure* online.

Declarations

Disclosure of Interest

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Data Availability

No further data are available. Individual patient data from the National Heart, Lung and Blood Institute Biologic Specimen and Data Repositories Information Coordinating Centre (NIH BioLINCC) are available via application (https://biolincc.nhlbi.nih.gov/home/). Individual patient data from the Beta-blockers in Heart Failure Collaborative Group are not available for sharing due to contractual requirements from the source data owners.

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