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Revisiting Race and the Benefit of RAS Blockade in Heart Failure
A Meta-Analysis of Randomized Clinical Trials

Li Shen, MBChB, PhD; Matthew M. Y. Lee, MBChB, PhD; Pardeep S. Jhund, MBChB, MSc, PhD; Christopher B. Granger, MD; Inder S. Anand, MD, PhD; Aldo P. Maggioni, MD; Marc A. Pfeffer, MD, PhD; Scott D. Solomon, MD; Karl Swedberg, MD, PhD; Salim Yusuf, DPhil; John J. V. McMurray, MD

IMPORTANCE Concerns have arisen that renin-angiotensin system (RAS) blockers are less effective in Black patients than non-Black patients with heart failure and reduced ejection fraction (HFrEF).

OBJECTIVE To determine whether the effects of RAS blockers on cardiovascular outcomes differ between Black patients and non-Black patients with HFrEF.

DATA SOURCES MEDLINE and Embase databases through December 31, 2023.

STUDY SELECTION Randomized trials investigating the effect of RAS blockers on cardiovascular outcomes in adults with HFrEF that enrolled Black and non-Black patients.

DATA EXTRACTION AND SYNTHESIS Individual-participant data were extracted following Preferred Reporting Items for Systematic Reviews and Meta-analyses Independent Personal Data (PRISMA-IPD) reporting guidelines. Effects were estimated using a mixed-effects model using a 1-stage approach.

MAIN OUTCOME AND MEASURE The primary outcome was first hospitalization for HF or cardiovascular death.

RESULTS The primary analysis, based on the 3 placebo-controlled RAS inhibitor monotherapy trials, included 8825 patients (9.9% Black). Rates of death and hospitalization for HF were substantially higher in Black than non-Black patients. The hazard ratio (HR) for RAS blockade vs placebo for the primary composite was 0.84 (95% CI, 0.69-1.03) in Black patients and 0.73 (95% CI, 0.67-0.79) in non-Black patients (*P* for interaction = .14). The HR for first HF hospitalization was 0.89 (95% CI, 0.70-1.13) in Black patients and 0.62 (95% CI, 0.56-0.69) in non-Black patients (*P* for interaction = .006). Conversely, the corresponding HRs for cardiovascular death were 0.83 (95% CI, 0.65-1.07) and 0.84 (95% CI, 0.77-0.93), respectively (*P* for interaction = .99). For total hospitalizations for HF and cardiovascular deaths, the corresponding rate ratios were 0.82 (95% CI, 0.66-1.02) and 0.72 (95% CI, 0.66-0.80), respectively (*P* for interaction = .27). The supportive analyses including the 2 trials adding an angiotensin receptor blocker to background angiotensin-converting enzyme inhibitor treatment (n = 16 383) gave consistent findings.

CONCLUSIONS AND RELEVANCE The mortality benefit from RAS blockade was similar in Black and non-Black patients. Despite the smaller relative risk reduction in hospitalization for HF with RAS blockade in Black patients, the absolute benefit in Black patients was comparable with non-Black patients because of the greater incidence of this outcome in Black patients.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: John J. V. McMurray, MD, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, United Kingdom (john.mcmurray@glasgow.ac.uk).

Although angiotensin-converting enzyme (ACE) inhibitors are a cornerstone of evidence-based therapy in patients with heart failure (HF), it has been suggested that Black patients may have less response to these drugs than do White patients. This hypothesis originated from post hoc analyses of the second Vasodilator Heart Failure Trial (V-HeFT II)[1] and the Studies of Left Ventricular Dysfunction (SOLVD)[2] and similar concerns have been voiced about antihypertensive efficacy.[2-5]

In a subgroup analysis of V-HeFT II,[1] it appeared that mortality was reduced by enalapril compared with hydralazine and isosorbide dinitrate in White men but not in Black men.[1,6] Specifically, among White patients, 90 of 292 treated with enalapril died whereas 112 of 282 treated with hydralazine and isosorbide dinitrate died. Among Black patients, 39 of 106 assigned to enalapril died compared with 39 of 109 treated with hydralazine and isosorbide dinitrate. However, the treatment-by-race interaction was not statistically significant (P = .09).[1] There was also no difference in the effect of treatment on HF hospitalization between White and Black patients.

No subgroup analysis of the effect of enalapril according to race has been published for SOLVD.[7,8] However, in a post hoc analysis, each of the 800 Black patients was matched with up to 4 White patients to examine the effect of enalapril compared with placebo on outcomes.[2] ACE-inhibitor treatment was associated with a lower rate of hospitalization for HF in White patients but not in Black patients. However, no difference in mortality was seen between racial groups.[2]

These data form the basis of the widely debated suggestion that renin-angiotensin system (RAS) blockers are less effective in Black patients than in White patients with HF and reduced ejection fraction (HFrEF).[9-12] The above findings are not robust, based on the number of events, the statistical methods used and the inconsistency of the results (for death compared with hospitalization). Therefore, we have reexamined the question of whether Black patients with HFrEF respond differently to RAS blockade by conducting a meta-analysis of individual patient data (IPD) from the prospective placebo-controlled trials investigating a RAS blocker and reporting mortality and hospitalization, including analysis of total (first and recurrent) hospitalizations for HF.

Key Points

Question Does the benefit of renin-angiotensin system (RAS) blockers in patients with heart failure and reduced ejection fraction differ between Black and non-Black patients?

Findings In this meta-analysis involving more than 16 000 patients from 5 randomized trials, the mortality benefit from RAS blockade was similar in Black and non-Black patients. Although the relative risk reduction in hospitalizations for heart failure was smaller in Black patients, the absolute benefit was comparable in the 2 groups given the greater incidence of hospitalization in Black patients.

Meaning RAS blockers are effective at improving cardiovascular outcomes in Black and non-Black patients with heart failure.

Methods

This study followed the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) statement and was prospectively registered in PROSPERO (CRD42024503987).[13]

Search Strategy and Study Selection

A systematic database search was performed by 2 authors (L.S. and M.M.Y.L.) using MEDLINE and EMBASE through December 31, 2023, without language restrictions (using the search strategy developed by L.S., M.M.Y.L., and J.J.V.M., which is provided in eAppendix 1 in Supplement 1).

Two authors (L.S. and M.M.Y.L.) independently screened all titles, abstracts, and full-text material to select studies that met the prespecified eligibility criteria (eMethods in Supplement 1). Discrepancies were resolved by consensus. The process and results of study selection are reported in eFigure 1 in Supplement 1. We identified 5 trials, namely SOLVD-Prevention[7] and SOLVD-Treatment,[8] along with the Candesartan in Heart Failure: Reduction in Mortality and Morbidity (CHARM)-Alternative,[14] CHARM-Added,[15] and the Valsartan Heart Failure Trial (Val-HeFT).[16]

Risk of Bias Assessment and Data Collection

Each trial was assessed with a low risk of bias (eFigure 2 in Supplement 1).[17] All patients provided written consent, and the study protocols were approved by the ethics committee at all participating centers.

Characteristics of the included studies were extracted using a standardized data extraction form (L.S.) and are presented in eTable 1 in Supplement 1. The IPD data of all included trials were provided by the principal investigators and checked for consistency before being transferred into STATA software for further management and analysis. Methods of data acquisition and management of the included trials are outlined in the study protocol (eAppendix 2 in Supplement 1).

Outcomes of Interest

The primary outcome was the composite of time to first hospitalization for HF or cardiovascular (CV) death. Secondary outcomes included first hospitalization for HF, CV death, and all-cause death, along with sudden death and pump failure death. We also examined total (first and recurrent) hospitalizations for HF and a composite of total hospitalizations for HF and CV deaths as described elsewhere[18] (eMethods in Supplement 1).

Subgroup and Classification of Race

The effect of RAS blockade vs placebo on all outcomes was examined according to the racial subgroup (ie, Black and non-Black groups). Reporting race and ethnicity was mandated by the US Food and Drug Administration because differences in response to medical products have been observed in racially and ethnically distinct subgroups of the US population.[19] In the trials analyzed, investigators were requested to ask patients to state which of the racial designations used best describes them (**Table 1**). Data on race and ethnic background

Table 1. Baseline Characteristics by Race in Patients With Heart Failure and Reduced Ejection Fraction

	Black patients (n = 873)	Non-Black patients (n = 7952)	Mean between-group difference (95% CI)
Age, mean (SD), y	57.0 (11.0)	61.4 (10.7)	−4.4 (−5.1 to −3.7)
Sex, No. (%)			
Men	631 (72.3)	6568 (82.6)	−10.3 (−13.4 to −7.2)
Women	242 (27.7)	1384 (17.4)	10.3 (7.2 to 13.4)
Body mass index, mean (SD)[a]	29.9 (6.2) [n = 72]	27.3 (4.8) [n = 1945]	2.5 (1.4 to 3.7)
Weight, mean (SD), kg	81.9 (17.6)	80.1 (15.3)	1.8 (0.7 to 2.9)
Blood pressure, mm Hg			
>150 Systolic, No. (%)	117 (13.4)	940 (11.8)	1.6 (−0.8 to 3.9)
Systolic, mean (SD)	126.4 (18.9)	126.3 (17.3)	0.1 (−1.2 to 1.3)
Diastolic, mean (SD)	79.5 (10.6)	77.1 (9.9)	2.4 (1.7 to 3.1)
Heart rate, mean (SD), beats/min	80.5 (13.0)	75.8 (13.1)	4.7 (3.8 to 5.6)
NYHA class, No. (%)[b]			
I	311 (35.7)	2793 (35.1)	0.5 (−2.8 to 3.8)
II	393 (45.1)	3429 (43.1)	1.9 (−1.6 to 5.4)
III	164 (18.8)	1613 (20.3)	−1.5 (−4.2 to 1.2)
IV	4 (0.5)	114 (1.4)	−1.0 (−1.5 to −0.5)
LVEF, mean (SD), %	26.1 (6.7)	27.8 (6.6)	−1.7 (−2.2 to −1.3)
Ischemic etiology, No. (%)	451 (51.7)	6284 (79.0)	−27.4 (−30.8 to −23.9)
Current smoking, No. (%)	265 (30.4)	1573 (19.8)	10.6 (7.4 to 13.7)
Medical history, No. (%)			
Hypertension	556 (63.7)	3111 (39.1)	24.6 (21.2 to 27.9)
Myocardial infarction	426 (48.8)	5890 (74.1)	−25.3 (−28.7 to −21.8)
Angina	408 (46.7)	4668 (58.7)	−12.0 (−15.4 to −8.5)
Diabetes	256 (29.3)	1602 (20.1)	9.2 (6.0 to 12.3)
CABG surgery or PCI	124 (14.2)	2584 (32.5)	−18.3 (−20.8 to −15.8)
Stroke	92 (10.5)	530 (6.7)	3.9 (1.8 to 6.0)
Atrial fibrillation or flutter	59 (6.8)	887 (11.2)	−4.4 (−6.2 to −2.6)
Treatment, No. (%)			
Diuretics	595 (68.2)	4039 (50.8)	17.4 (14.1 to 20.6)
Loop	480 (55.0)	3291 (41.4)	13.6 (10.1 to 17.1)
Thiazide	123 (14.1)	731 (9.2)	4.9 (2.5 to 7.3)
Potassium-sparing	46 (5.3)	943 (11.9)	−6.6 (−8.2 to −4.9)
Digoxin	350 (40.1)	2823 (35.5)	4.6 (1.2 to 8.0)
Long-acting nitrates	322 (36.9)	2783 (35.0)	1.9 (−1.5 to 5.3)
Antiplatelets	247 (28.3)	4153 (52.2)	−23.9 (−27.1 to −20.7)
Calcium channel blockers	234 (26.8)	2369 (29.8)	−3.0 (−6.1 to 0.1)
β-Blockers	119 (13.6)	2199 (27.7)	−14.0 (−16.5 to −11.5)
Anticoagulants	111 (12.7)	1415 (17.8)	−5.1 (−7.4 to −2.7)
Antiarrhythmic agents	106 (12.1)	1366 (17.2)	−5.0 (−7.4 to −2.7)
Hydralazine	60 (6.9)	192 (2.4)	4.5 (2.7 to 6.2)
Pacemaker use	25 (2.9)	391 (4.9)	−2.1 (−3.3 to −0.8)
Electrocardiography, No. (%)			
Left ventricular hypertrophy	144 (16.5)	657 (8.3)	8.2 (5.7 to 10.8)
Q wave	141 (16.2)	2343 (29.5)	−13.3 (−16.0 to −10.7)
Atrial fibrillation	42 (4.8)	589 (7.4)	−2.6 (−4.1 to −1.1)
Symptoms and signs, No. (%)			
S_3 gallop	161 (18.4)	983 (12.4)	6.1 (3.4 to 8.8)
Peripheral edema	120 (13.7)	1013 (12.7)	1.0 (−1.4 to 3.4)
Jugular venous distention	81 (9.3)	477 (6.0)	3.3 (1.3 to 5.3)
Rales	53 (6.1)	709 (8.9)	−2.8 (−4.5 to −1.1)

(continued)

Table 1. Baseline Characteristics by Race in Patients With Heart Failure and Reduced Ejection Fraction (continued)

	Black patients (n = 873)	Non-Black patients (n = 7952)	Mean between-group difference (95% CI)
Laboratory tests			
Sodium, mean (SD), mmol/L	139.6 (3.2)	140.1 (3.0)	−0.5 (−0.7 to −0.3)
Potassium, mean (SD), mmol/L	4.2 (0.5)	4.3 (0.4)	−0.1 (−0.1 to −0.1)
Hematocrit, mean (SD), %	41.0 (4.7)	42.7 (4.5)	−1.7 (−2.0 to −1.3)
Creatinine, mean (SD), mg/dL[c]	1.27 (0.36) [n = 839]	1.17 (0.29) [n = 6481]	0.10 (0.08 to 0.12)

Abbreviations: CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

SI conversion factor: to convert creatinine from mg/dL to µmol/L, multiply by 88.4.

[a] Height and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) were not available in Studies of Left Ventricular Dysfunction (SOLVD)–Prevention and SOLVD-Treatment.

[b] NYHA functional classification grades the severity of functional limitations in patients with heart failure from class I to IV with a higher class indicating more severe limitations, specifically: I, no limitation of physical activity (ordinary physical activity does not cause undue fatigue, palpitation, dyspnea); II, slight limitation of physical activity (comfortable at rest; ordinary physical activity results in fatigue, palpitation, dyspnea); III, marked limitation of physical activity (comfortable at rest, less than ordinary activity causes fatigue, palpitation, or dyspnea); IV, unable to carry on any physical activity without discomfort (symptoms of heart failure at rest, discomfort increases if any physical activity is undertaken).

[c] Creatinine was available in 4158 (98.3%) patients in SOLVD-Prevention, 2502 (97.3%) in SOLVD-Treatment, and 660 (32.5%) in Candesartan in Heart Failure: Reduction in Mortality and Morbidity (CHARM)-Alternative.

were obtained at baseline from the clinical trial case report forms, in which participants could be identified as American Indian, Asian, Black, Caucasian, Hispanic, or other in SOLVD-Prevention and SOLVD-Treatment. In CHARM-Alternative and CHARM-Added, patients could be identified as Arab or Middle Eastern, Black, European origin, Oriental, Malay, South Asian, or other. In Val-HeFT, patients were identified as Black, Oriental, White or Caucasian, or other. The race categories described are the original designations used in the trials analyzed and *other* was a predefined category in all 5 trials.

Statistical Analysis

The primary analysis was performed in the combined cohort of SOLVD-Prevention, SOLVD-Treatment, and CHARM-Alternative ie, the 3 trials in which patients were not receiving background RAS inhibitor treatment. The supportive analysis further included CHARM-Added and Val-HeFT, in which patients had an angiotensin receptor blocker added to a background ACE inhibitor. However, the total events-supportive analysis only included 4 of the 5 trials because data from Val-HeFT was not obtained.

Baseline characteristics are presented as means and SDs for continuous variables, and percentages for categorical variables.

A 1-stage IPD meta-analysis was used to examine the effect of RAS inhibitor treatment on all outcomes, according to the intention-to-treat principle, overall and by race subgroup. Time-to-first events were evaluated using Kaplan-Meier curves and Cox proportional-hazards models, and total events were analyzed using Nelson-Aalen curves and the semiparametric proportional rates method of Lin et al.[20] Both models were based on a mixed-effects model with randomized treatment as a fixed effect and trial as a random effect. For recurrent events, we calculated the absolute risk reduction by multiplying the event rate in the placebo group by the corresponding relative risk reduction with treatment. In a sensitivity analysis, a 2-stage IPD random-effects meta-analysis was performed to examine the robustness of the findings and heterogeneity across studies using the I^2 statistic.[21]

Publication bias was examined for the primary composite and all-cause death. There was no indication of publication bias for both outcomes with *P* values >.6 from the Egger test and symmetrical funnel plots (eFigure 3 in Supplement 1),[22] although the power of these tests may be limited given the small number of studies identified. The proportional hazards assumption was assessed using Schoenfeld residuals, and violation was only observed for first hospitalization for HF and the primary composite in the non-Black group. When examining graphically using log-log survival plots, the curves were rather parallel over time, suggesting the assumptions should still be valid (eTable 2 and eFigure 4 in Supplement 1).

We evaluated changes in the estimated glomerular filtration rate (eGFR), using the 2021 creatinine-only Chronic Kidney Disease Epidemiology Collaboration equation,[23] and systolic and diastolic blood pressures (BPs) from baseline using a mixed model for repeated measurements (eMethods in Supplement 1). We assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (eTable 3 in Supplement 1).[24] Complete case analysis was used for these analyses unless otherwise specified. A 2-sided *P* value <.05 was considered significant. All analyses were performed using Stata version 17 (StataCorp).

Results

The primary analysis of the 3 placebo-controlled RAS inhibitor monotherapy trials included 873 Black patients (9.9%) and 7952 non-Black patients (90.1%). Of the non-Black patients, 7515 (85.2% of the total population) were categorized as White; 152 Asian (1.7%); and 285 other race (3.2%) (eTable 1 in Supplement 1). The median follow-up was 34 months (IQR, 24-43 months) overall, 32 (IQR, 23-42) months for Black patients, and 34 months (IQR, 25-43 months) for non-Black patients. In the supportive 5-trial analysis, there were a total of 1344 Black patients (8.2%) and 15 039 non-Black patients (91.8%), with an

Table 2. Mean Daily Dose of Renin-Angiotensin System Inhibitor Achieved Relative to the Target Dose and Proportion of Patients Reaching the Target Dose

Visit	Black patients			Non-Black patients			Difference in differences (95% CI)	Interaction *P* value[b]
	RAS inhibitors (n = 433)[a]	Placebo (n = 440)[a]	Difference (95% CI)	RAS inhibitors (n = 3976)[a]	Placebo (n = 3976)[a]	Difference (95% CI)		
Daily dose achieved (as a percentage) relative to the target daily dose, mean (SD) [No. of patients][c]								
1: 6 wk	82.1 (28.3) [403]	84.8 (26.1) [396]	−2.7 (−6.5 to 1.1)	75.0 (31.2) [3694]	81.0 (28.4) [3677]	−6.0 (−7.4 to −4.7)	3.3 (−1.0 to 7.7)	.13
2: 4-6 mo[d]	83.0 (28.4) [371]	89.6 (22.5) [363]	−6.6 (−10.3 to −2.9)	80.6 (30.3) [3455]	87.7 (25.6) [3399]	−7.1 (−8.4 to −5.7)	0.5 (−3.8 to 4.7)	.83
3: 8-10 mo[d]	84.6 (27.3) [349]	90.0 (22.4) [332]	−5.4 (−9.2 to −1.7)	81.3 (30.0) [3247]	88.9 (24.6) [3153]	−7.6 (−9.0 to −6.3)	2.2 (−2.1 to 6.5)	.31
Patients reaching the target daily dose, No (%)/total[c]								
1: 6 wk	281 (69.7)/403	291 (73.5)/396	−3.7 (−10.0 to −2.5)	2170 (58.7)/3694	2485 (67.6)/3677	−8.8 (−11.0 to −6.6)	5.1 (−1.5 to 11.7)	.23
2: 4-6 mo[d]	267 (72.0)/371	296 (81.5)/363	−9.6 (−15.6 to −3.5)	2392 (69.2)/3455	2721 (80.1)/3399	−10.8 (−12.9 to −8.8)	1.2 (−5.2 to 7.6)	.85
3: 8-10 mo[d]	260 (74.5)/349	274 (82.5)/332	−8.0 (−14.2 to −1.9)	2285 (70.4)/3247	2592 (82.2)/3153	−11.8 (−13.9 to −9.8)	3.8 (−2.7 to 10.3)	.35

Abbreviation: RAS, renin-angiotensin system.

[a] The analysis was performed among those patients taking therapy at each of the follow-up visits. Patients who were censored or had discontinued the study drug by the time of the visit examined were not included. Drug dose was available in 96.5% of patients who had not been censored by 6 weeks, and the corresponding number was 93.5% at 4 to 6 months, and 90.9% at 8 to 10 months.

[b] For differences in the dose between placebo and RAS inhibitors in Black patients vs non-Black patients.

[c] The target daily dose of enalapril was 20 mg per day in the Studies of Left Ventricular Dysfunction (SOLVD) trial, and for candesartan was 32 mg per day in the Candesartan in Heart Failure: Reduction in Mortality and Morbidity (CHARM) trial.

[d] Visit 2 was at 4 months after randomization in SOLVD and 6 months in CHARM, and visit 3 was at 8 months in SOLVD and 10 months in CHARM.

overall median follow-up of 30 months (IQR, 21-41 months) (eTable 4 in Supplement 1).

Baseline Characteristics

Black patients were younger (57.0 vs 61.4 years), and more often women (27.7% vs 17.4%) than non-Black patients (Table 1). They had a higher mean body mass index, diastolic BP, and serum creatinine level; had a higher prevalence of hypertension (63.7% vs 39.1%) and diabetes (29.3% vs 20.1%), but less often an ischemic etiology (51.7% vs 79.0%) compared with non-Black patients. Although New York Heart Association class distribution did not differ significantly, Black patients had a lower left ventricular ejection fraction, had more symptoms and signs of HF, and were prescribed a diuretic and digoxin more often but a β-blocker less often than non-Black patients.

The overall clinical profile (and differences between patient groups) was almost identical in the supportive 5-trial dataset (eTable 4 in Supplement 1). The baseline characteristics were broadly similar between randomized treatment in each patient group, both for the primary and supportive analyses (eTables 5 and 6 in Supplement 1).

Treatment Dosing and Changes in Blood Pressure and eGFR After Randomization

Over the first 6 weeks, the dose of RAS inhibitor achieved was somewhat higher in Black than non-Black patients, although the difference narrowed thereafter (**Table 2**).

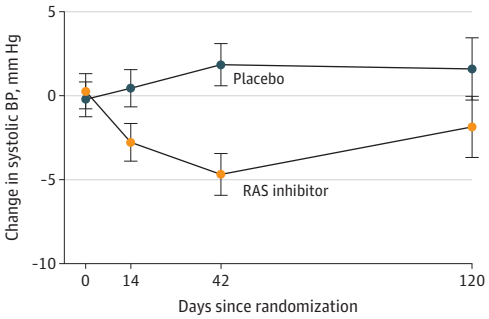
The placebo-corrected decrease in systolic BP in response to RAS blocker treatment at 6 weeks was 7.0 mm Hg (95% CI, 4.9-9.1 mm Hg) in Black patients and 7.0 mm Hg (95% CI, 6.3-7.6 mm Hg) in non-Black patients (**Figure 1** and eFigure 5 in Supplement 1). Thereafter, the reduction in systolic BP remained similar between patient groups. There was no interaction between race and the effect of treatment on either systolic or diastolic BP (both *P* for interaction >.40). Likewise, the pattern of change in eGFR by treatment was essentially the same in Black patients and non-Black patients (*P* for interaction = .91; eFigure 6 in Supplement 1).

Clinical Outcomes

Overall, Black patients experienced an approximately 50% higher risk of cardiovascular outcomes than non-Black patients (**Table 3** and **Figure 2**). The rate of the composite of first hospitalization for HF or CV death, in the placebo arm, was 21.6 per 100 person-years in Black patients and 14.7 per 100 person-years in non-Black patients. The corresponding rates of first hospitalization for HF were 14.0 and 9.4 per 100 person-years, respectively. This pattern was also seen for CV death and all-cause death. For the primary composite, the unadjusted HR for RAS inhibitor, compared with placebo, was 0.84 (95% CI, 0.69-1.03) in Black patients and 0.73 (95% CI, 0.67-0.79) in non-Black patients (*P* for interaction = .14). This was primarily driven by the effect on the first hospitalization for HF, with an unadjusted HR of 0.89 (95% CI, 0.70-1.13) in Black patients and 0.62 (95% CI, 0.56-0.69) in non-Black patients (*P* for interaction = .006). However, the benefit of RAS inhibitor on CV death was similar between patient groups, with an unadjusted HR of 0.83 (95% CI, 0.65-1.07) and 0.84 (95% CI, 0.77-0.93) in Black

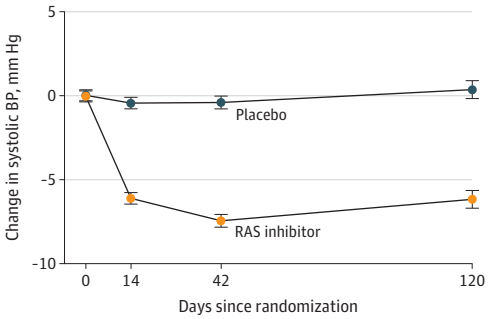
Figure 1. Change in Blood Pressure From Baseline During Study Visits

A Black patients systolic BP



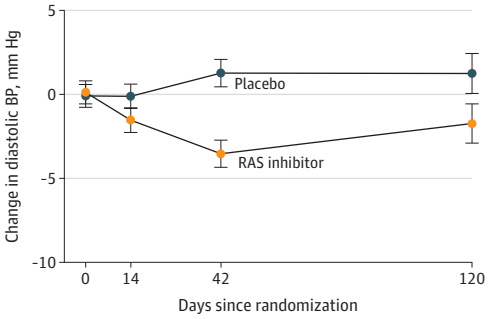
No. of patients				
Placebo	439	416	401	369
RAS inhibitor	431	405	411	387
Least squares mean change from baseline, mm Hg				
Placebo	Reference	0.7	2.1	1.8
RAS inhibitor	Reference	-3.0	-5.0	-2.1
Between-group difference (95% CI), mm Hg		-3.7 (-5.7 to -1.7)	-7.0 (-9.1 to -4.9)	-3.9 (-6.6 to -1.2)

B Non-Black patients systolic BP



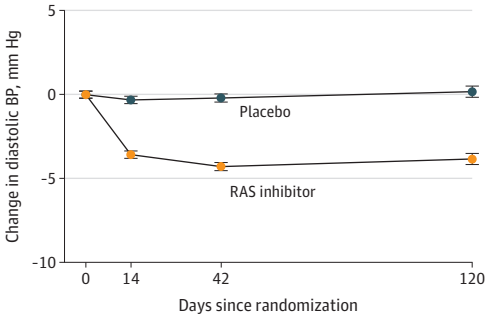
No. of patients				
Placebo	3954	3866	3792	3616
RAS inhibitor	3958	3883	3840	3686
Least squares mean change from baseline, mm Hg				
Placebo	Reference	-0.5	-0.4	0.3
RAS inhibitor	Reference	-6.1	-7.4	-6.1
Between-group difference (95% CI), mm Hg		-5.6 (-6.2 to -5.0)	-7.0 (-7.6 to -6.3)	-6.5 (-7.2 to -5.7)

C Black patients diastolic BP



No. of patients				
Placebo	439	416	401	369
RAS inhibitor	431	404	411	387
Least squares mean change from baseline, mm Hg				
Placebo	Reference	0	1.4	1.3
RAS inhibitor	Reference	-1.7	-3.7	-1.9
Between-group difference (95% CI), mm Hg		-1.6 (-3.0 to -0.3)	-5.0 (-6.4 to -3.6)	-3.2 (-4.9 to -1.4)

D Non-Black patients diastolic BP



No. of patients				
Placebo	3954	3865	3791	3616
RAS inhibitor	3956	3881	3838	3683
Least squares mean change from baseline, mm Hg				
Placebo	Reference	-0.3	-0.2	0.2
RAS inhibitor	Reference	-3.6	-4.3	-3.8
Between-group difference (95% CI), mm Hg		-3.3 (-3.7 to -2.9)	-4.1 (-4.5 to -3.7)	-4.0 (-4.5 to -3.5)

Data are from the combined Studies of Left Ventricular Dysfunction (SOLVD)–Prevention and SOLVD-Treatment and the Candesartan in Heart Failure: Reduction in Mortality and Morbidity (CHARM)–Alternative dataset. Change in systolic blood pressure over time by renin-angiotensin system (RAS) treatment in Black patients and non-Black patients. Data of between-group differences are shown as mean difference (95% CI). Systolic blood pressure (BP) was available from 99.5% of patients at baseline, 97.6% of patients who had not been censored by 14 days, 97.0% at 42 days, and 95.1% at 120 days after randomization (*P* for interaction = .45). The corresponding numbers for diastolic BP were 99.5%, 97.6%, 97.0%, and 95.0%, respectively. Blood pressure at 120 days after randomization was not collected in the CHARM trial; thus, the measurements at 6 months were used instead (*P* for interaction = .61). Data points represent the mean; whiskers 95% CIs. The distribution of changes is shown in eFigure 5 in Supplement 1.

and non-Black patients, respectively (*P* for interaction = .99), as was the case for all-cause death (*P* for interaction = .89) and the 2 modes of death (both *P* for interaction >.50, eTable 7 in Supplement 1).

For the total hospitalizations for HF, the event rate in the placebo arm was 25.2 per 100 person-years in Black patients and 15.8 per 100 person-years in non-Black patients (Table 3 and Figure 2). The unadjusted rate ratio was 0.82 (95% CI, 0.62-1.07) in Black patients and 0.66 (95% CI, 0.58-0.75) in non-Black patients (*P* for interaction = .16), with 4.5 and 5.4 fewer hospitalizations for HF, respectively, per 100 patient-years of treatment. For total hospitalizations for HF and CV deaths, the unadjusted rate ratio was 0.82 (95% CI, 0.66-1.02) in Black patients and 0.72 (95% CI, 0.66-0.80) in non-Black patients (*P* for interaction = .27), with 6.6 and 6.7 fewer events, respectively, per 100 patient-years of treatment.

The adjustment for other prognostic variables made little difference to these results (Table 3). The supportive 5-trial analyses and the 2-stage meta-analysis showed consistent findings (eTables 8 and 9 and eFigure 7 in Supplement 1). The

Table 3. Clinical Outcomes According to Race and Renin-Angiotensin System Inhibitor Treatment in Patients With Heart Failure and Reduced Ejection Fraction

	Event No. (person-years)		Rate (95% CI) per 100 person-years			RAS inhibitors vs placebo, unadjusted HR or RR (95% CI)[a]	*P* value[b]	RAS inhibitors vs placebo, adjusted HR or RR (95% CI)[a,c]	*P* value[b]
	RAS inhibitors	Placebo	RAS inhibitors	Placebo	Difference (95% CI)				
First hospitalization for heart failure or cardiovascular death									
Black patients (n = 873)	190 (1007.3)	206 (952.2)	18.9 (16.4 to 21.7)	21.6 (18.9 to 24.8)	−2.8 (−6.8 to 1.2)	HR, 0.84 (0.69 to 1.03)	.14	HR, 0.85 (0.69 to 1.04)	.07
Non-Black patients (n = 7952)	1107 (10 329.1)	1399 (9525.7)	10.7 (10.1 to 11.4)	14.7 (13.9 to 15.5)	−4.0 (−5.0 to −3.0)	HR, 0.73 (0.67 to 0.79)		HR, 0.70 (0.65 to 0.76)	
First hospitalization for heart failure									
Black patients (n = 873)	128 (1007.3)	133 (952.2)	12.7 (10.7 to 15.1)	14.0 (11.8 to 16.6)	−1.3 (−4.5 to 2.0)	HR, 0.89 (0.70 to 1.13)	.006	HR, 0.90 (0.70 to 1.15)	.002
Non-Black patients (n = 7952)	600 (10 329.1)	892 (9525.7)	5.8 (5.4 to 6.3)	9.4 (8.8 to 10.0)	−3.5 (−4.3 to −2.8)	HR, 0.62 (0.56 to 0.69)		HR, 0.59 (0.53 to 0.66)	
Cardiovascular death									
Black patients (n = 873)	117 (1177.6)	130 (1135.0)	9.9 (8.3 to 11.9)	11.5 (9.6 to 13.6)	−1.5 (−4.2 to 1.1)	HR, 0.83 (0.65 to 1.07)	.99	HR, 0.82 (0.64 to 1.06)	.91
Non-Black patients (n = 7952)	766 (11 082.4)	881 (10 782.4)	6.9 (6.4 to 7.4)	8.2 (7.6 to 8.7)	−1.3 (−2.0 to −0.5)	HR, 0.84 (0.77 to 0.93)		HR, 0.84 (0.76 to 0.92)	
All-cause death									
Black patients (n = 873)	132 (1177.6)	144 (1135.0)	11.2 (9.5 to 13.3)	12.7 (10.8 to 14.9)	−1.5 (−4.3 to 1.3)	HR, 0.85 (0.67 to 1.07)	.89	HR, 0.84 (0.66 to 1.07)	.99
Non-Black patients (n = 7952)	898 (11 082.4)	996 (10 782.4)	8.1 (7.6 to 8.7)	9.2 (8.7 to 9.8)	−1.1 (−1.9 to −0.4)	HR, 0.87 (0.80 to 0.96)		HR, 0.87 (0.80 to 0.95)	
Total hospitalization for heart failure									
Black patients (n = 873)	251 (1177.6)	286 (1135.0)	21.3 (18.8 to 24.1)	25.2 (22.4 to 28.3)	−3.9 (−7.8 to 0.1)	RR, 0.82 (0.62 to 1.07)	.16	RR, 0.81 (0.62 to 1.07)	.12
Non-Black patients (n = 7952)	1167 (11 082.4)	1706 (10 782.4)	10.5 (9.9 to 11.2)	15.8 (15.1 to 16.6)	−5.2 (−6.3 to −4.3)	RR, 0.66 (0.58 to 0.75)		RR, 0.65 (0.57 to 0.74)	
Total hospitalization for heart failure and cardiovascular deaths									
Black patients (n = 873)	367 (1177.6)	415 (1135.0)	31.2 (28.1 to 34.5)	36.6 (33.2 to 40.3)	−5.4 (−10.1 to −0.7)	RR, 0.82 (0.66 to 1.02)	.27	RR, 0.82 (0.65 to 1.02)	.21
Non-Black patients (n = 7952)	1925 (11 082.4)	2579 (10 782.4)	17.4 (16.6 to 18.2)	23.9 (23.0 to 24.9)	−6.5 (−7.8 to −5.3)	RR, 0.72 (0.66 to 0.80)		RR, 0.71 (0.65 to 0.78)	

Abbreviations: HR, hazard ratio; RAS, renin-angiotensin system; RR, rate ratio.

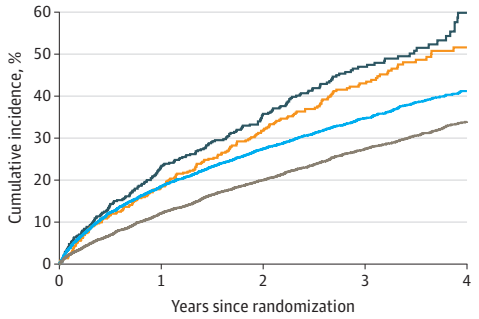
[a] A 1-stage individual patient data meta-analysis was based on a mixed-effects model with randomized treatment as a fixed effect and trial as a random effect.

[b] *P* values are for interaction between racial groups (Black vs non-Black patients) and RAS inhibitor treatment (yes vs no) on each clinical outcome.

[c] Adjustment model: age, sex, heart rate, systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction, New York Heart Association class, ischemic etiology, history of myocardial infarction, hypertension, diabetes and atrial fibrillation or flutter, baseline use of β-blockers and diuretics, and serum creatinine value with simple imputation of serum creatinine.

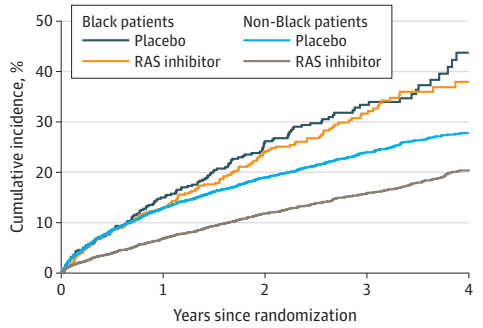
Figure 2. Cumulative Incidences and Cumulative Hazard Estimates for Clinical Outcomes

A First hospitalization for heart failure or cardiovascular death



No. at risk					
Black patients					
Placebo	440	337	250	117	33
RAS inhibitor	433	350	267	139	53
Non-Black patients					
Placebo	3976	3219	2558	1462	422
RAS inhibitor	3976	3466	2821	1627	496

B First hospitalization for heart failure



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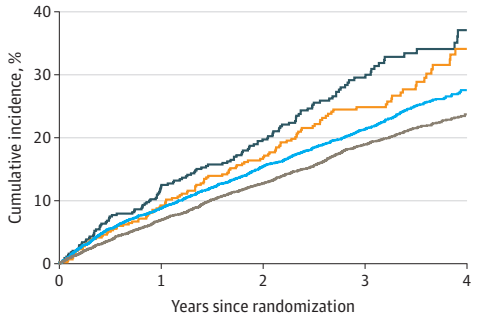
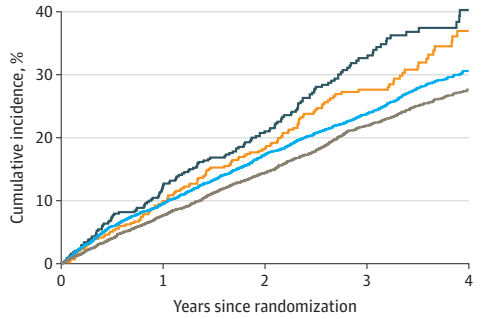
RAS inhibitor	433	350	267	139	53
Non-Black patients					
Placebo	3976	3219	2558	1462	422
RAS inhibitor	3976	3466	2821	1627	496

C Cardiovascular death



No. at risk					
Black patients					
Placebo	440	386	313	159	57
RAS inhibitor	433	390	326	184	68
Non-Black patients					
Placebo	3976	3596	2979	1777	515
RAS inhibitor	3976	3667	3086	1815	560

D All-cause death



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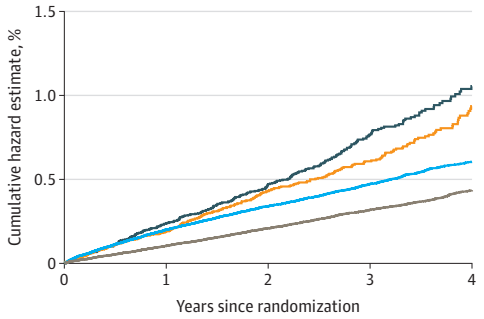
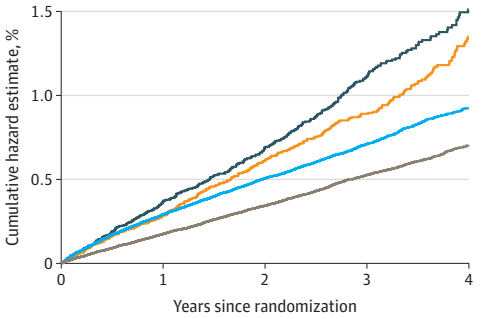
RAS inhibitor	433	390	326	184	68
Non-Black patients					
Placebo	3976	3596	2979	1777	515
RAS inhibitor	3976	3667	3086	1815	560

E Total hospitalizations for heart failure



No. at risk					
Black patients					
Placebo	440	386	313	159	57
RAS inhibitor	433	390	326	184	68
Non-Black patients					
Placebo	3976	3596	2979	1777	515
RAS inhibitor	3976	3667	3086	1815	560

F Total hospitalizations for heart failure and cardiovascular deaths



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Data are from the combined Studies of Left Ventricular Dysfunction (SOLVD)–Prevention and SOLVD-Treatment and the Candesartan in Heart Failure: Reduction in Mortality and Morbidity (CHARM)–Alternative dataset. RAS indicates renin-angiotensin system.

heterogeneity of treatment effects across studies was small (I^2 <20%) for all outcomes in both patient groups and overall (eFigure 7 in Supplement 1), except for first hospitalization for HF in which considerable heterogeneity was observed in the overall population (I^2 = 61%), consistent with the interaction for this outcome described above.

Discussion

In this meta-analysis, there was no evidence of diminished mortality benefit from RAS blockade in Black patients compared with non-Black patients. By contrast, the relative risk reduction with RAS blockade on the first hospitalization for HF was smaller in Black patients; as a result, the effect of RAS blockers on the composite of HF hospitalization or CV death also tended to be less in Black patients. Nevertheless, because rates of death and HF hospitalization were 40% to 50% higher in Black patients than non-Black patients, the absolute benefit from RAS blockade in Black patients was greater for mortality and comparable for total hospitalizations for HF.

As mentioned in the Introduction, a subgroup analysis of V-HeFT II and a matched-cohort analysis of the SOLVD trials, coupled with reports of diminished blood pressure–lowering efficacy of RAS blockers in Black patients with hypertension, are the basis of the concern about the benefit of RAS blockade in Black patients with HF. This analysis, using a larger dataset, demonstrates that the reported lack of effect of RAS blockers on mortality in Black patients with HF is incorrect. The magnitude of the effect of RAS blockade on mortality was the same in Black patients as in non-Black patients and consistent with the benefit in the overall cohort.[8,25,26] As noted previously, the mortality rate in Black patients was around 40% higher than in non-Black patients; thus, the absolute risk reduction with RAS blockade was even greater in Black patients than in non-Black patients (approximately 2 vs 1 fewer deaths per 100 person-years of treatment).[11,27-29]

Conversely, the relative risk reduction in hospitalization for HF with RAS blockers in Black patients was smaller than in non-Black patients, with a significant race-by-treatment interaction. In the conventional time-to-first event analysis, the benefit of a RAS blocker on the first HF hospitalization in Black patients was modest (relative risk reduction ≈ 11%) and not statistically significant. However, when methods counting total hospitalizations were used, with more statistical power, a greater effect (relative risk reduction ≈ 18%) of RAS blockade on total HF hospitalizations was observed in Black patients, although this was about half the effect observed in non-Black patients (relative risk reduction ≈ 34%). The disparity in benefit between the patient groups was further narrowed when all HF hospitalizations and cardiovascular deaths were combined and analyzed. Consistent with other studies,[30-33] the rate of total HF hospitalizations was substantially higher in Black patients than non-Black patients, and this led to a comparable absolute benefit for Black patients and non-Black patients.

This apparent difference between effects on mortality and hospitalization is puzzling and difficult to explain, given that these 2 outcomes are related and usually reduced in tandem by efficacious therapies. One possibility is that while an effect on mortality unequivocally reflects the pharmacological effect of RAS blockade on a consequence of the disease, hospitalization for HF may be influenced by other factors including access to ambulatory compared with hospital care, quality of care, level of education, environmental and socioeconomic factors, and other considerations such as implicit bias.[34-36] Some recent observations suggest a narrowing or even absence of the gap in mortality between Black patients and non-Black patients, but a persisting difference in hospitalization rates shows that these outcomes can be dissociated.[33,37-39] Prior studies have suggested possible differences in response to RAS blockade in Black patients compared with non-Black patients, particularly related to the antihypertensive effect of these agents. In turn, biological explanations have been proposed for these disputed findings, including possible genetic differences.[29,34-36] However, groups defined by race are not genetically distinct, and it is now generally accepted that race is a social construct with no basis in genetics.[5,40-43] Consistent with this view, no difference was found in the reduction in BP or eGFR between Black patients and non-Black patients randomized to a RAS blocker. These findings also support the interpretation that the mortality reduction with RAS blockade is similar in both patient groups.

The substantial absolute reduction in the total HF hospitalizations with RAS blockade in Black patients, coupled with an equivalent reduction in mortality in Black patients and non-Black patients, emphasizes the value of this cornerstone treatment in HFrEF in both patient groups. There has been concern that the uncertainty about the benefit of RAS blockers has contributed to the undertreatment of Black patients with these drugs, and it is hoped that this meta-analysis will allay such concerns.[11,12,44]

Limitations

Even though this meta-analysis included all the large placebo-controlled outcome trials with a RAS blocker in HFrEF, the number of Black patients was still modest, reflecting the underrepresentation of Black patients in clinical trials.[27] The eligibility criteria used in these trials may affect the generalizability of these results to real-world populations. The trials included in this study are also not reflective of contemporary clinical practice, although there is no reason to believe that the effects of RAS blockade would be different today from when the trials were conducted. The differences in the baseline characteristics and outcomes of Black patients compared with non-Black patients are also consistent with more contemporary studies, although, as mentioned, the gap in mortality may be decreasing, as may also be the gap in treatment.[32,33,35] Since the conduct of the trials analyzed in this study, understanding of the importance of socioeconomic status and other social determinants of health to race-based outcomes has increased.[5,40-43] The social and structural factors that may underlie any race-related differences in outcomes could not be fully examined because such information was not collected.[36,45] Future studies of this type should prospectively collect information on the social determinants of health.

Conclusions

In this IPD meta-analysis, Black patients had higher rates of deaths and HF hospitalizations than did non-Black patients. The mortality benefit from RAS blockade was similar in Black and non-Black patients, with consequent large absolute risk reductions in Black patients. Although the effect of RAS blockade on hospitalizations for HF was smaller in Black patients, for unexplained reasons, the absolute benefit on this outcome was comparable between patient groups given the higher rate in Black patients.

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Author Affiliations: School of Clinical Medicine, Hangzhou Normal University, Hangzhou, China (Shen); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, United Kingdom (Shen, Lee, Jhund, McMurray); Duke Clinical Research Institute, Durham, North Carolina (Granger); Division of Cardiology, Duke University School of Medicine, Durham, North Carolina (Granger); Veterans Affairs Medical Center and University of Minnesota, Minneapolis (Anand); ANMCO Research Center, Heart Care Foundation, Florence, Italy (Maggioni); Division of Cardiology, Garibaldi-Nesima Hospital, Catania, Italy (Maggioni); Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Pfeffer, Solomon); Department of Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg, Sweden (Swedberg); Population Health Research Institute and Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada (Yusuf).

Author Contributions: Drs Shen and McMurray had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Shen, Lee, Pfeffer, Solomon.
Acquisition, analysis, or interpretation of data: Shen, Lee, Jhund, Granger, Anand, Maggioni, Swedberg, Yusuf, McMurray.
Drafting of the manuscript: Shen.
Critical review of the manuscript for important intellectual content: Lee, Jhund, Granger, Anand, Maggioni, Pfeffer, Solomon, Swedberg, Yusuf, McMurray.
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