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CLINICAL RESEARCH

Income Inequality and Outcomes in Heart Failure

A Global Between-Country Analysis

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ABSTRACT

OBJECTIVES This study examined the relationship between income inequality and heart failure outcomes.

BACKGROUND The income inequality hypothesis postulates that population health is influenced by income distribution within a society, with greater inequality associated with worse outcomes.

METHODS This study analyzed heart failure outcomes in 2 large trials conducted in 54 countries. Countries were divided by tertiles of Gini coefficients (where 0% represented absolute income equality and 100% represented absolute income inequality), and heart failure outcomes were adjusted for standard prognostic variables, country per capita income, education index, hospital bed density, and health worker density.

RESULTS Of the 15,126 patients studied, 5,320 patients lived in Gini coefficient tertile 1 countries (coefficient: <33%), 6,124 patients lived in tertile 2 countries (33% to 41%), and 3,772 patients lived in tertile 3 countries (>41%). Patients in tertile 3 were younger than tertile 1 patients, were more often women, and had less comorbidity and several indicators of less severe heart failure, yet the tertile 3-to-1 hazard ratios (HRs) for the primary composite outcome of cardiovascular death or heart failure hospitalization were 1.57 (95% confidence interval [CI]: 1.38 to 1.79) and 1.48 for all-cause death (95% CI: 1.29 to 1.71) after adjustment for recognized prognostic variables. After additional adjustments were made for per capita income, education index, hospital bed density, and health worker density, these HRs were 1.46 (95% CI: 1.25 to 1.70) and 1.30 (95% CI: 1.10 to 1.53), respectively.

CONCLUSIONS Greater income inequality was associated with worse heart failure outcomes, with an impact similar to those of major comorbidities. Better understanding of the societal and personal bases of these findings may suggest approaches to improve heart failure outcomes. (J Am Coll Cardiol HF 2019;7:336–46) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Heart failure (HF) is now recognized as a major public health problem not only in Western nations but also in low- and middle-income countries, reflecting the demographic changes and the epidemiological transition to noncommunicable diseases occurring in the latter countries (1). The growing recognition of the international importance of HF has been accompanied by studies highlighting the considerable differences in HF outcomes that exist among countries (2,3). Understanding the basis of these differences may help in tackling this increasing global problem. Some of the geographical variations in identified outcomes are attributable to differences in recognized prognostic factors such age, HF severity, and comorbidity. Other factors may also be pertinent, such as income inequality, which varies considerably internationally and is often particularly marked in low- and middle-income countries. The income inequality hypothesis postulates that population health is influenced by the degree to which income is unevenly distributed within a society (4,5). This hypothesis was developed to explain why large differences in population health are still observed in developed countries with high levels of income, as measured by gross domestic product (GDP) per capita (6,7). A variety of studies has shown a negative correlation between income inequality and life expectancy, infant mortality, and the incidence, prevalence, and burden of several diseases. The PARADIGM-HF (Prospective comparison of ARNI [Angiotensin Receptor Neprilysin Inhibitor] with ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and morbidity in Heart Failure) and the ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with Heart Failure) trials were 2 of the largest clinical trials in patients with HF with reduced ejection fraction (HFrEF) (8,9). The present study analyzed a pooled cohort of 15,216 participants from 54 of the 55 countries worldwide who were enrolled in the 2 trials to examine the potential association among different levels of income inequality and clinical characteristics and outcomes in patients with HFrEF.

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METHODS

TRIALS AND PARTICIPANTS. The design, baseline characteristics, and outcomes of the PARADIGM-HF and ATMOSPHERE trials have been published and are briefly described here (8,9). The inclusion and exclusion criteria of the 2 trials were almost identical. Patients were eligible at screening if they were ≥18 years of age and they had New York Heart Association (NYHA) functional class II to IV, a left ventricular ejection fraction (LVEF) ≤35% (changed from ≤40% initially PARADIGM-HF by amendment), elevated concentrations of natriuretic peptide (the cutoff level was independent of atrial fibrillation), and were taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) with a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist, if indicated. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure (SBP) <95 mm Hg (<90 mm Hg in ATMOSPHERE), an estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m^2 (<35 in ATMOSPHERE), and a potassium concentration of >5.4 mmol/l (>5.2 in ATMOSPHERE). The trial was approved by the ethics committees at all participating centers in 47 countries in PARADIGM-HF and in 43 countries in ATMOSPHERE. All patients provided written informed consent.

On trial entry, ongoing therapy with an ACE inhibitor or ARB was stopped, and patients entered a sequential run-in, first receiving enalapril, followed by sacubitril/valsartan in PARADIGM-HF and enalapril, followed by the combination of enalapril plus aliskiren in ATMOSPHERE. Patients who tolerated both of the run-in periods were randomly assigned to receive double-blinded therapy with sacubitril/valsartan or enalapril in a 1:1 ratio in PARADIGM-HF or enalapril or aliskiren or both drugs in a 1:1:1 ratio in ATMOSPHERE. PARADIGM-HF ran from December 2009 to May 2014, and ATMOSPHERE ran from May 2009 to October 2015 (median follow-up intervals were 27 months and 36.6 months, respectively) (8,9).

STUDY GROUPS. The impact of income inequality was evaluated using the Gini coefficient, which is derived from the Lorenz curve (Online Figure S1), in which 0 (0%) indicates absolute income equality and 1 (100%) indicates absolute income inequality. For most countries, Gini coefficients were obtained from the United Nations Development Programme (UNDP) (10). Data from 2003 were used to account for a lag effect, whereby a state of inequality dating back 15 years might have had a stronger association with health than current income inequality (11). For

ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

TABLE 1 Baseline Characteristics, Clinical Features, Investigations, and Treatment According to Tertiles of Gini Coefficient

	Gini Tertile 1 Least Inequality (n = 5,320)	Gini Tertile 2 Intermediate Group (n = 6,124)	Gini Tertile 3 Greatest Inequality (n = 3,772)
Baseline characteristics			
Gini coefficient	<33	33–41	>41
Number of countries	18	19	17
Age, yrs	66.3 ± 10.3	62.8 ± 11.6	61.0 ± 12.2
Age group, yrs			
≤40	78 (1.5)	254 (4.1)	215 (5.7)
41-55	690 (13.0)	1,255 (20.5)	963 (25.5)
56-70	2,556 (48.0)	2,932 (47.9)	1,716 (45.5)
>70	1,996 (37.5)	1,683 (27.5)	878 (23.3)
Females	1,118 (21.0)	1,273 (20.8)	936 (24.8)
Region			
North America	0 (0.0)	779 (12.7)	0 (0.0)
Latin America	0 (0.0)	187 (3.1)	2,365 (62.7)
Western Europe and other	2,315 (43.5)	1,328 (21.7)	311 (8.2)
Central Europe	2,570 (48.3)	2,136 (34.9)	64 (1.7)
Asia-Pacific	435 (8.2)	1,694 (27.7)	1,032 (27.4)
Per capita income, US$	31,582 ± 18,675	20,714 ± 17,704	9,980 ± 5,706
Percentage of national GDP spent on health care	9.1 ± 1.9	7.8 ± 3.4	6.8 ± 1.5
HDI	0.890 (0.834-0.920)	0.803 (0.676-0.877)	0.737 (0.723-0.780)
Education index	0.847 (0.822-0.898)	0.814 (0.635-0.852)	0.664 (0.616-0.709)
Life index	0.924 (0.847-0.935)	0.817 (0.740-0.931)	0.855 (0.834-0.863)
Income index	0.865 (0.816-0.917)	0.830 (0.657-0.879)	0.725 (0.719-0.785)
Hospital beds per 1,000	6.4 (6.0-8.2)	2.9 (1.0-6.5)	2.5 (1.6-3.8)
Health workers per 1,000*	6.0 (4.7-8.7)	4.5 (1.4-6.1)	1.9 (1.8-4.1)
SBP, mm Hg	125 ± 16.9	122 ± 16.5	120 ± 16.3
HR, beats/min	71.5 ± 12.8	72.5 ± 11.8	71.8 ± 12.2
BMI, kg/m^2	28.6 ± 5.2	27.7 ± 5.8	26.9 ± 5.2
Weight category†			
Underweight	37 (0.7)	179 (2.9)	88 (2.3)
Normal	1,267 (23.8)	1,877 (30.6)	1,335 (35.4)
Overweight	2,158 (40.6)	2,182 (35.6)	1,448 (38.4)
Obese	1,853 (34.8)	1,869 (30.5)	894 (23.7)
Medical history			
Hypertension	3,733 (70.2)	4,072 (66.5)	2,324 (61.6)
Diabetes	1,804 (33.9)	2,011 (32.8)	954 (25.3)
Atrial fibrillation, ECG	1,704 (32.0)	1,254 (20.5)	639 (16.9)
Atrial fibrillation history	2,496 (46.9)	2,030 (33.2)	885 (23.5)
Unstable angina	626 (11.8)	788 (12.9)	264 (7.0)
Myocardial infarction	2,292 (43.1)	3,021 (49.3)	1,111 (29.5)
Stroke	490 (9.2)	466 (7.6)	245 (6.5)
COPD	789 (14.8)	820 (13.4)	222 (5.9)
Renal disease	846 (15.9)	929 (15.2)	233 (6.2)
ECG findings			
LBBB	1,023 (19.2)	1,219 (21.6)	815 (21.6)
RBBB	601 (11.3)	564 (9.2)	405 (10.7)
QRS duration, ms	119.9 ± 34.7	114.9 ± 35.5	116.5 ± 36.7
Smoking/alcohol			
Smoking status			
Never smoked	2,536 (47.7)	3,401 (55.5)	2,129 (56.4)
Ex-smoker	1,970 (37.0)	1,949 (31.8)	1,175 (31.2)
Current smoker	814 (15.3)	774 (12.6)	468 (12.4)
Alcohol, drinks/day‡			
<1	4,368 (82.1)	5,496 (89.8)	3,492 (92.6)
1-2	788 (14.8)	521 (8.5)	204 (5.4)
>2	164 (3.1)	105 (1.7)	76 (2.0)

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TABLE 1 Continued

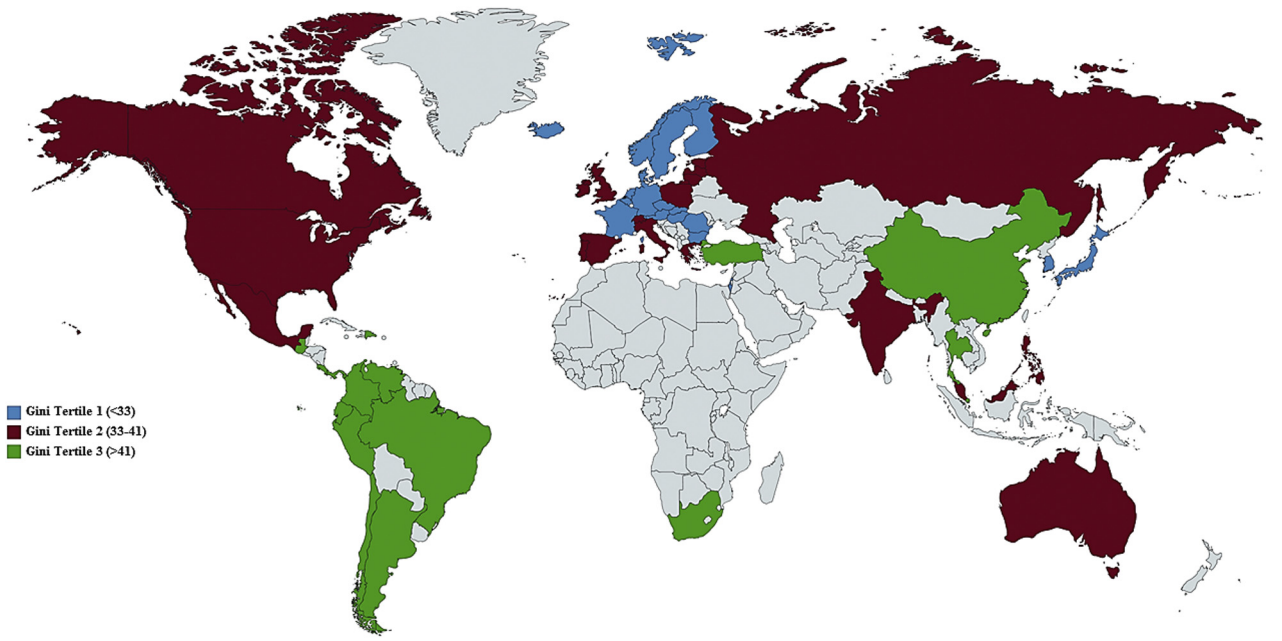
	Gini Tertile 1 Least Inequality (n = 5,320)	Gini Tertile 2 Intermediate Group (n = 6,124)	Gini Tertile 3 Greatest Inequality (n = 3,772)
Heart failure: clinical features, investigations, drugs and devices			
Gini coefficient	<33	33–41	>41
Time since HF diagnosis, yrs			
<1	1,526 (28.7)	1,928 (31.5)	1,357 (36.0)
1-5	1,964 (36.9)	2,278 (37.2)	1,514 (40.1)
>5	1,829 (34.4)	1,915 (31.3)	901 (23.9)
HF cause			
Ischemic	3,251 (61.1)	4,107 (67.1)	1,521 (40.3)
Nonischemic	1,573 (29.6)	1,428 (23.3)	1,726 (45.8)
Unknown	496 (9.3)	589 (9.6)	525 (1.4)
Prior hospitalization for HF	3,331 (62.6)	3,686 (60.2)	2,292 (60.8)
NYHA functional class§			
I/II	3,748 (68.6)	4,264 (69.7)	3,231 (85.7)
III	1,627 (30.6)	1,793 (29.3)	520 (13.8)
IV	45 (0.9)	58 (1.0)	17 (0.5)
KCCQ, clinical summary score	77.1 (60.4–90.0)	76.0 (58.9–89.6)	87.5 (75.0–95.8)
Dyspnea on effort	4,642 (87.3)	5,387 (88.2)	2,997 (79.5)
Orthopnea	267 (5.0)	428 (7.0)	272 (7.2)
PND	345 (6.5)	276 (4.5)	129 (3.4)
Edema	1,213 (22.8)	1,437 (23.5)	489 (13.0)
Third heart sound	409 (7.7)	748 (12.2)	200 (5.3)
JVD	590 (11.1)	457 (7.5)	422 (11.2)
LVEF	29.9 ± 5.7	28.9 ± 6.1	28.0 ± 6.0
LVH	852 (16.0)	1,693 (27.6)	950 (25.2)
NT-proBNP, pg/ml	1,358 (766–2,540)	1,424 (755–2,816)	1,500 (803–3,130)
Hemoglobin, g/l	140.6 ± 14.8	136.7 ± 17.0	138.8 ± 16.0
eGFR, ml/min per 1.73 m^2	68.1 ± 19.8	70.3 ± 22.3	74.7 ± 24.6
eGFR, <60 ml/min per m^2	1,861 (35.0)	1,994 (32.6)	981 (26.0)
Drug, devices, other therapy			
Diuretics	4,342 (81.6)	4,903 (80.1)	2,945 (78.1)
Digitalis	1,374 (25.8)	1,955 (31.9)	1,395 (37.0)
Beta-blocker	4,995 (93.9)	5,591 (91.3)	3,489 (92.5)
MRA	2,381 (44.8)	2,660 (43.4)	2,162 (57.3)
ACE inhibitor pre-randomization	4,772 (89.7)	5,434 (88.7)	3,191 (84.6)
ARB pre-randomization	621 (11.7)	717 (11.7)	590 (15.6)
Statin	3,146 (59.1)	3,741 (61.1)	1,437 (38.1)
Anticoagulants	2,426 (45.6)	1,717 (28.0)	631 (16.7)
Aspirin	2,469 (46.4)	3,393 (55.4)	1,978 (52.4)
Prior PCI	1,384 (26.0)	1,232 (20.1)	510 (13.5)
Prior CABG	969 (18.2)	1,015 (16.6)	278 (7.4)
Conventional pacemaker	780 (14.7)	709 (11.6)	297 (7.9)
ICD or CRT-D	1,131 (21.3)	986 (16.1)	165 (4.4)
CRT-P or CRT-D	442 (8.3)	417 (6.8)	101 (2.7)

Values are n (%), median (IQR), or mean ± SD. *Taking into account only physician and nurses/midwives' density per 1,000 population. †29 were missing. ‡One drink equals 12 oz beer, 8 oz malt liquor, 5 oz wine, 1.5 ounces, or a shot of spirits or liquor. §13 values were missing.

ACE inhibitor = angiotensin angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; D = defibrillator; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; GDP = gross domestic product; HDI = human development index; HF = heart failure; HR = heart rate; ICD = implantable cardioverter cardioverter-defibrillator; IQR = inter quartile range; JVD = jugular venous distension; KCCQ = Kansas City Cardiomyopathy Questionnaire; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N terminal-pro B-type natriuretic peptide; NYHA = New York Heart Association; P = pacemaker; PCI = percutaneous coronary intervention; PND = paroxysmal nocturnal dyspnea; RBBB = right bundle branch block; SBP = systolic blood pressure; US$ = U.S. dollars.

countries where a Gini coefficient for 2003 was unavailable, a value from the year closest to 2003 was used. Gini coefficients for Hong Kong, Japan, Korea, and Singapore were derived from other sources. Taiwan was excluded from the analysis because social indicators could not be derived from UNDP and because reports from other sources were inconsistent and unreliable.

FIGURE 1 World Map Showing Participating Countries According to Tertiles of Gini Coefficient



Patients were divided into 3 groups by tertiles according to the distribution of Gini coefficients. Group 1 countries (least inequality) had a Gini coefficient of <33, group 2 consisted of those countries with Gini coefficients between 33 and 41 and group 3 countries (greatest inequality) had Gini coefficients of >41. The association between income inequality and outcomes was also tested using the Gini coefficient as a continuous variable.

OTHER SOCIOECONOMIC INDICATORS. To adjust for other socioeconomic variables, additional information was also collected, including national per capita income (in US$ from the World Bank) (12), hospital bed density (from The World Factbook) (13), and health worker density (from the World Health Organization) (14) per 1,000 population. The education index was derived from the Human Development Index from the UNDP database (15), for further analysis of outcomes, as discussed subsequently. To derive health worker density, the average densities of physicians and nurses/midwives were used as figures for other types of health care workers that were not uniformly available from all countries. All figures were ascertained for 2013 or the closest year to 2013.

OUTCOMES. The primary outcome for both trials was the composite value of the first hospitalization for HF or cardiovascular death. In the present study, the associations between income inequality, as reflected in the Gini coefficient, the risk of the primary outcome and each of its components, and all-cause mortality were investigated. All endpoints were adjudicated by the same clinical endpoint committee according to pre-specified criteria.

STATISTICAL ANALYSIS. Baseline characteristic values are proportions, mean ± SD, and median (interquartile range [IQR]). Statistical methods used to analyze baseline characteristics were analysis of variance, the chi-square test, and the Kruskal-Wallis rank test for nonparametric values. Competing risk regression was carried out using the Fine-Gray model to analyze the outcomes of interest, using 3 models (16). All-cause mortality was analyzed using Cox regression. Model 1 was used to calculate the crude hazard ratio (HR) for each outcome. Model 2 fitted age, sex, heart rate, SBP, body mass index, NYHA functional class, LVEF, eGFR, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Model 3 fitted per capita income, education index, hospital bed density, and health worker density, in addition to the variables used in Model 2. Results from a multilevel Cox regression model were compared with those from another Cox model, which adjusted only for region, and found very little variability to account for random effects (17). Consequently, all models were adjusted for region along with randomized treatment at baseline. Schoenfeld residuals were used to test the proportional hazards assumption. Values of $p < 0.05$ were considered significant. All analyses were

conducted using Stata version 14 software (StataCorp, College Station, Texas).

RESULTS

Overall, 15,126 patients from 54 countries were included (Table 1, Online Table S1). The median Gini coefficient was 35.1 (range 25.9 to 64.8; 25th and 75th percentile: 31.9 and 40.9, respectively). The mean was 38.1 (9). The highest Gini coefficient tertile (tertile: 3; coefficient: >41; greatest inequality) included 3,772 patients in 17 countries from 4 of the 5 global regions (North America was excluded) (Figure 1). The middle tertile (33 to 41) included 6,124 individuals in 19 countries from all 5 regions, and the lowest tertile (tertile: 1; coefficient: <33; least inequality) included 5,320 patients in 18 countries from 3 of the 5 regions (North America and Latin America were excluded) (Figure 1).

As the Gini coefficient increased, the human development index, the per capita income, the proportion of GDP spent on health care, and the hospital bed density decreased (Table 1).

BASELINE CHARACTERISTICS. Patient characteristics varied considerably by income inequality (Table 1). A higher proportion of patients in Gini tertile 3 countries were women (24.8% vs. 21.0%, respectively, in tertile 1, and 20.8%, respectively, in tertile 2). Patients in Gini tertile 3 countries were younger (61 vs. 66 and 63 years of age, respectively), and fewer were obese (23.7% vs. 34.8% and 30.5%, respectively). Gini tertile 3 countries had the highest proportion of people who never smoked and lower consumption of alcohol, whereas tertile 1 countries had the highest proportions of smokers and heavier consumers of alcohol.

COMORBIDITIES. Gini tertile 3 countries had the lowest prevalence of all recorded comorbid conditions, including hypertension, diabetes, atrial fibrillation, stroke, chronic obstructive pulmonary disease, and renal disease (Table 1). By contrast, Gini tertile 1 countries had the highest prevalence of all comorbid conditions, with the single exception of unstable angina (but not myocardial infarction [MI]), which was slightly more common in tertile 2 than in tertile 1 countries.

HEART FAILURE CHARACTERISTICS. In keeping with the pattern of comorbidity, Gini tertile 3 patients were the least likely to have HF caused by ischemia (Table 1). Gini tertile 3 patients had the highest proportion of patients with a more recent diagnosis of HF, although all groups had a similar proportion of patients with a prior HF hospitalization. Gini tertile 3 patients had the highest proportion of patients in NYHA functional classes I/II and the highest (best) Kansas City Cardiomyopathy Questionnaire scores. LVEF differed little across Gini tertiles. However, the median NT-proBNP concentration was highest in Gini tertile 3 patients (1,500 pg/ml; IQR: 803 to 3,130 pg/ml), and the lowest level was seen in tertile 1 patients (1,358 pg/ml; IQR: 766 to 2,540 pg/ml).

Gini tertile 3 patients had the lowest prevalence of dyspnea on effort, paroxysmal nocturnal dyspnea, third heart sound, and peripheral edema. Patients in tertile 3 also had the lowest SBP (120 vs. 125 mm Hg, respectively, in tertile 1, and 122 mm Hg in tertile 2). Gini tertile 3 patients had the highest average eGFR level, and tertile 1 patients had the lowest eGFR (Table 1).

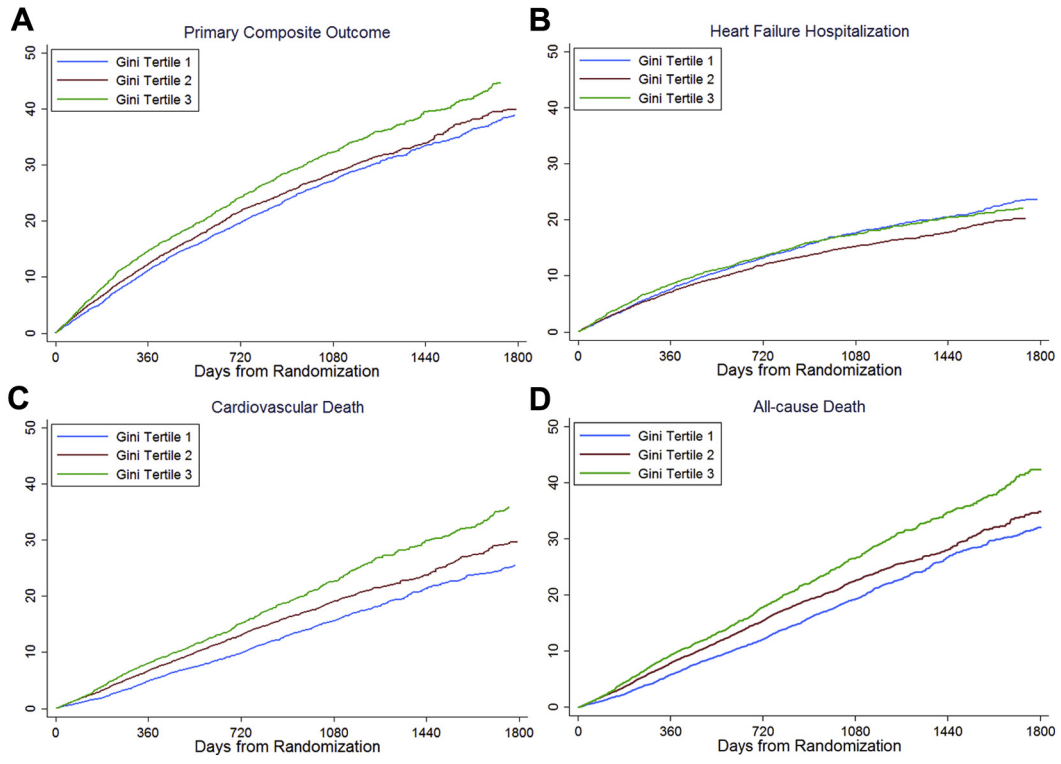
TABLE 2 Clinical Outcomes of the PARADIGM-HF and ATMOSPHERE Trials According to Tertiles of Gini Coefficient

	Gini Tertile 1	Gini Tertile 2	Gini Tertile 3
	Least Inequality (n = 5,320)	Intermediate Group (n = 6,124)	Greatest Inequality (n = 3,772)
Gini coefficient	<33	33-41	>41
Primary composite outcome			
Events	1,480 (27.8)	1,694 (27.7)	1,138 (33.7)
Event rates per 100 person-yrs (95% CI)	10.9 (10.4–11.5)	11.7 (11.2–12.3)	13.7 (12.9–14.5)
Unadjusted HR	1.00 (reference)	1.06 (0.99–1.15)	1.56 (1.39–1.76)
Adjusted HR-1*	1.00 (reference)	1.03 (0.95–1.11)	1.57 (1.38–1.79)
Adjusted HR-2†	1.00 (reference)	0.99 (0.91–1.08)	1.46 (1.25–1.70)
HF Hospitalization			
Events	941 (17.7)	900 (14.7)	611 (16.2)
Event rates per 100 person-yrs (95% CI)	6.9 (6.5–7.4)	6.2 (5.8–6.6)	7.4 (6.8–8.0)
Unadjusted HR	1.00 (reference)	0.83 (0.75–0.92)	1.57 (1.36–1.81)
Adjusted HR-1*	1.00 (reference)	0.81 (0.72–0.90)	1.52 (1.30–1.77)
Adjusted HR-2†	1.00 (reference)	0.85 (0.76–0.96)	1.92 (1.58–2.33)
CV death			
Events	881 (16.6)	1,143 (18.7)	801 (21.2)
Event rates per 100 person-yrs (95% CI)	5.9 (5.6–6.3)	7.3 (6.9–7.7)	8.9 (8.3–9.5)
Unadjusted HR	1.00 (reference)	1.24 (1.13–1.37)	1.50 (1.29–1.74)
Adjusted HR-1*	1.00 (reference)	1.21 (1.10–1.33)	1.55 (1.32–1.82)
Adjusted HR-2†	1.00 (reference)	1.12 (1.01–1.25)	1.35 (1.12–1.62)
All-cause death			
Events	1,097 (20.6)	1,349 (22.0)	938 (24.9)
Event rates per 100 person-yrs (95% CI)	7.4 (7.0–7.8)	8.6 (8.2–9.1)	10.4 (9.8–11.1)
Unadjusted HR	1.00 (reference)	1.20 (1.10–1.30)	1.44 (1.25–1.65)
Adjusted HR-1*	1.00 (reference)	1.18 (1.08–1.28)	1.48 (1.29–1.71)
Adjusted HR-2†	1.00 (reference)	1.13 (1.02–1.24)	1.30 (1.10–1.53)

Values are n (%), median (IQR), or mean ± SD. Events are reported as n (%) and as rate per 100 patient-years (95% CI). Primary outcome was tested for competing risk of all non-CV death; first hospitalization for HF was tested for competing risk of all-cause death; and CV death was tested for competing risk of all non-CV death. All models were adjusted for region and randomized treatment at baseline. *Adjusted for age, sex, HR, SBP, BMI, NT-proBNP, eGFR, LVEF, and NYHA functional class. †Adjusted for age, sex, HR, SBP, BMI, NT-proBNP, eGFR, LVEF, NYHA functional class, per capita income, education index, hospital bed density, and health worker density.

CI = confidence interval; CV = cardiovascular; other abbreviations as in Table 1.

FIGURE 2 Cumulative Incidence Plots



Cumulative incidence plot of **(A)** primary composite outcome; **(B)** hospitalization for HF; **(C)** cardiovascular death; and **(D)** Kaplan-Meier plot of all-cause death. HF = heart failure.

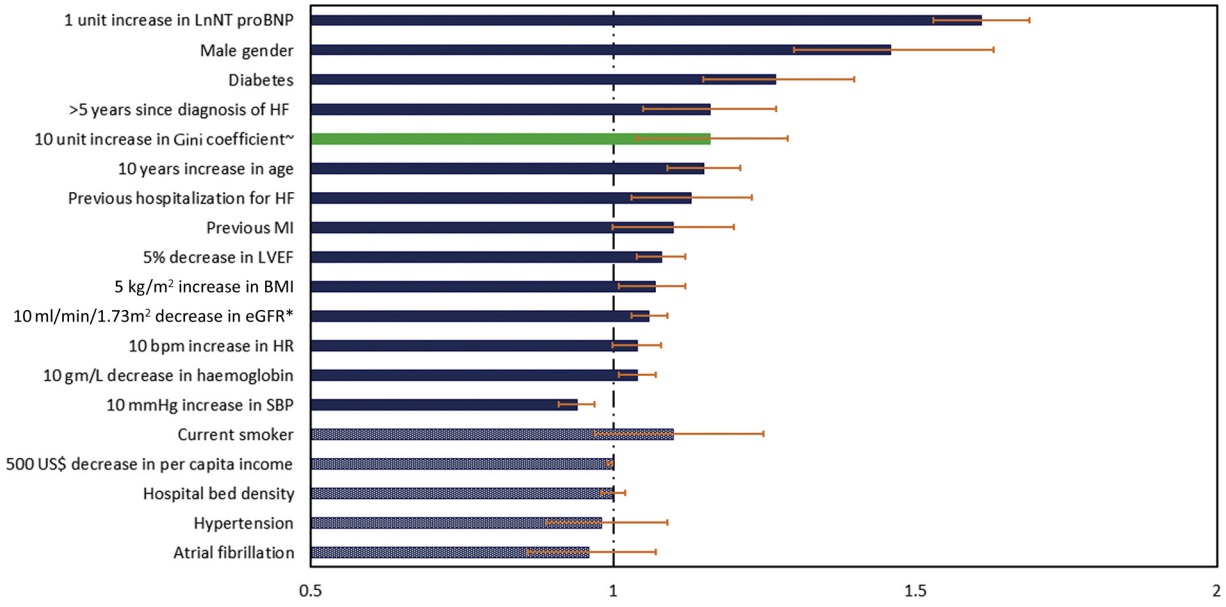
BASELINE DRUGS, DEVICES, AND OTHER THERAPIES. Gini tertile 3 patients were least often treated with a diuretic and most often treated with a mineralocorticoid receptor antagonist and digoxin (despite the lower prevalence of atrial fibrillation). Pre-trial use of an ARB (instead of an ACE inhibitor) was most common in tertile 3 countries (Table 1). Use of devices was lowest in tertile 3 patients, who had the use of cardiac resynchronization therapy with a pacemaker (CRT-P) or a defibrillator (CRT- D) was 2.7%, and the use of an implantable cardioverter-defibrillator or CRT-D was 4.4%, respectively; whereas the use of these devices was intermediate in tertile 2 patients (6.8% and 16.1%, respectively) and highest in individuals in tertile 1 countries (8.3% and 21.3%, respectively). Prior coronary revascularization (and statin therapy) showed similar patterns (Table 1).

COMPOSITE OUTCOME AND MORTALITY. Patients in Gini tertile 3 had the highest rate of primary composite outcome (13.7 per 100 person-years), and the rate was intermediate in tertile 2 (11.7 per 100 person-years) and lowest in tertile 1 (10.9 per 100 person-years) (Table 2, Figure 2). This trend was also observed for both of the rates of cardiovascular and all-cause death, which were highest in tertile 3 patients (8.9 and 10.4, respectively) and lowest in tertile 1 patients (5.9 and 7.4, respectively) (Table 2, Figure 2).

In the model that was adjusted for conventional prognostic variables, including NT-proBNP, patients in Gini tertile 3 remained at significantly higher risk of the primary composite outcome (57% higher risk) and of cardiovascular and all-cause death (55% and 48% higher, respectively) (Table 2).

When country per capita income, education index, hospital bed density, and health worker density were added to the multivariate models, the elevated risk in Gini tertile 3 patients was attenuated but remained significant (46%, 35%, and 30% higher for the primary composite outcome, cardiovascular death, and all-cause mortality, respectively) (Table 2). When the Gini coefficient was considered a continuous rather than a categorical variable, it remained an independent predictor of outcomes. Each 10-point increase in Gini coefficient was associated with a higher risk of

FIGURE 3 Multivariate Model of Predictors of Cardiovascular Death in HF



~On a scale of 0 to 100; *for eGFR <90 ml/min/1.73 m^2. **Hatched bars** = statistically nonsignificant values. BMI = body mass index; eGFR = estimated glomerular filtration rate; HF = heart failure; LnNT proBNP = log transformed N -terminal pro-B-type natriuretic peptide; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SBP = systolic blood pressure; US$ = United States dollars.

cardiovascular death (HR: 1.16; 95% confidence interval [CI]: 1.04 to 1.29; p = 0.005) and death from any cause (HR: 1.15; 95% CI: 1.04 to 1.26; p = 0.006) (Online Table S2, **Figure 3**). As seen in **Figure 3**, the impact of a 10-point increase in Gini coefficient on cardiovascular death was greater than that of most other predictive variables, including advancing age and previous MI.

HOSPITAL ADMISSION FOR HEART FAILURE. The unadjusted rate of HF hospitalization was highest in Gini tertile 3 patients but intermediate in tertile 1 rather than tertile 2 patients, as it was for the other outcomes. In adjusted model 2, risk of hospital admission for HF was 92% higher in Gini tertile 3 than in tertile 1 patients (HR: 1.92; 95% CI: 1.58 to 2.33) (**Table 2**).

DISCUSSION

In this study of 15,126 HFrEF patients from 54 countries, a statistically significant and clinically substantial association was found between income inequality and patient characteristics, and disease outcomes. These differences persisted after adjustments were made for recognized, patient-level prognostic variables, as well as for country per capita income.

Over the past 20 years, a substantial body of evidence has accrued in support of an association between income inequality and a variety of measurements of population health. The income inequality hypothesis states that an individual's health is affected not only by his or her own income but also by the distribution of income in that person's society, especially in high-income countries. Consistent with this hypothesis, countries sharing the same GDP may have quite different health outcomes, reflecting the distribution of income within those societies. That is, it appears that it is not only the wealth of a society but the distribution of wealth within that society that influences health. Although these relationships are well established for broad health outcomes such as childhood and overall mortality, there are few studies of specific diseases, especially cardiovascular disease (CVD). However, in one analysis involving 78 countries, income inequality was independently and positively associated with disability-adjusted life years and mortality related to coronary heart disease (CHD) and coronary risk factors (18). In another investigation, confined to the United States, a state-level analysis of the National Longitudinal Mortality Study showed that a 0.1-U higher Gini coefficient predicted a 1% higher probability of dying from CHD (19). The present study extended this

examination of the relationship between income disparity and cardiovascular health to HF.

The baseline characteristics, medical history, and background treatment of patients differed markedly according to income inequality but perhaps not predictably or intuitively, given the association between higher Gini coefficient and worse outcomes. For example, patients in countries with the highest Gini coefficient (tertile 3; greatest income inequality) were, on average, 5 years younger than those in the lowest tertile countries, and they were more often women who had less comorbidity, had an ischemic cause less often, had HF more recently diagnosed, had a better NYHA functional class profile and Kansas City Cardiomyopathy Questionnaire score, and had the highest mean eGFR. These are all features that were expected to track with better rather than worse outcomes, which could be attributable to the fact that patients in Gini tertile 3 were younger (20). Indeed, only a few variables associated with a poor prognosis were more unfavorable in the Gini coefficient tertile 3 patients, including an average LVEF that was lower (−1.9%) in tertile 3 patients than in tertile 1 patients, as was SBP (−5.2 mm Hg), whereas median NT-proBNP levels were somewhat higher (+142 pg/ml). There were also some treatment differences among the groups that were more expected, for example, digoxin (which is inexpensive) was used most often in tertile 3 patients, whereas devices (which are more expensive) were used much less often.

Even after correcting for patient-level biological characteristics known to predict outcomes, including the most powerful of these, NT-proBNP, patients in Gini tertile 3 had considerably higher mortality than those in tertile 1. Indeed, the adjusted HR was 1.48 (95% CI: 1.29 to 1.71) for all-cause death and 1.55 (95% CI: 1.32 to 1.82) for death from cardiovascular causes. Because population health and life-expectancy are also associated with overall country affluence, per capita income, which attenuated but did not eliminate the relationship between income disparity and mortality (with a remaining excess risk ranging from 20% to 30%), was also adjusted for. This disconnect between mortality and clinical presentation in Gini tertile 3 is difficult to explain but is most likely a function of the unfavorable effects of income inequality.

Additional adjustments for education index, hospital bed density, and physician density also did not attenuate the greater risk of the composite outcome among patients in Gini tertile 3, with a fully adjusted HR of 1.46 (95% CI: 1.25 to 1.70). When the risk of HF hospitalization alone was examined (but accounting for the competing risk of death), it was also found to be highest in countries with the greatest income disparity. Those countries also had the lowest bed density, suggesting that admission rates are not just a function of bed availability.

The large size of the "effect" of income inequality on HF outcomes is worthy of comment. The adjusted risks of the fatal outcomes were approximately 20% to 30% higher in individuals living in the tertile of countries with the widest income distribution. This magnitude of differences was similar to or greater than that attributable to other major comorbidities such as diabetes or previous MI. The risk associated with a 10-U increase in Gini coefficient was also analyzed, noting that the differences between the median coefficient in tertiles 1 and 3 was 20 U. The excess risk for cardiovascular mortality per 10-U increase in Gini coefficient was 16%, similar to the risk associated with a 10% decrease in LVEF, a decrease of 27 mm Hg in SBP, or a decrease of 27 ml/min per 1.73 m^2 in eGFR.

Countries were divided according to thirds of Gini coefficient, giving tertiles of <33%, 33% to 41%, and >41%. There is generally no consensus for the categorization of nations according to Gini coefficient, although in a study by Kim and colleagues (18), which examined CHD and stroke, countries were divided into "low" (<0.38), "medium" (95% CI: 0.38 to 0.55), and "high" (>0.55) Gini coefficient groups (using a scale of 0 to 1.0). In a meta-analysis of 9 multilevel longitudinal studies including nearly 60 million participants, Kondo et al. (21) reported a relative risk of 1.08 (95% CI: 1.06 to 1.10) for all-cause mortality per 0.05-U increase in Gini coefficient (using a scale of 0 to 1.0). Analysis of the present study showed an equivalent increase in Gini coefficient (5 points on a scale of 0 to 100) was associated with an HR of 1.07 (95% CI: 1.02 to 1.12; $p = 0.006$); that is, an excess risk of similar magnitude.

Of course, the key question about the present findings, and those about income inequality health hypothesis generally, is why should greater income disparity be associated with worse health outcomes? Many theories have been expounded. One way to consider these outcomes is under the broad headings of "societal-structural" and "psychosocial" explanations.

The "societal-structural" explanations are numerous and complex, and not all are necessarily relevant to outcomes in patients with an established clinical condition (as opposed to the future development of disease) (22,23). Many of these explanations focus on the corrosive effects of income inequality on society, leading to loss of social cohesion and divergence between the interests of the rich and those of the poor. It is argued that income inequality leads to the decreased

willingness of societies to invest in social services and welfare programs, broad access to health care services, and safety nets (24,25). These effects may lead to distortions of health care priorities and spending and can be exacerbated by geographical concentrations of hospitals and physicians in more affluent areas, with provision of medically unnecessary services and performance of discretionary procedures in these areas. Conversely, there may be underinvestment in health care infrastructure and resources in areas of greater need, with reduced access to and affordability of health care for the neediest (25). Potentially, each of these factors could lead to a higher prevalence of disease, delayed care, more advanced disease at presentation, more preventable hospital admissions, and ultimately, more premature deaths. It is also easy to see how a syndrome as complicated as HF, with its need for integration of primary and secondary health care services, multidisciplinary management programs, appropriate exercise prescription, complex polypharmacy and attendant electrolyte monitoring, tailored treatment of physical and psychological comorbidity, appropriate selection of devices, and ultimately, provision of palliative care may be particularly affected by gaps in services and aggravated by failure of social and family networks related to loss of social cohesion (26).

Some of these societal issues may also be greater in low- and middle-income countries undergoing epidemiologic transitions from infectious diseases to noncommunicable diseases (27). Here, health strategies and policies need to change, but these countries often display a high level of income disparity, despite (or because of) accelerated economic growth in many cases (28).

Among the psychosocial explanations, the one that is of most interest in HF is the belief that chronic stress as a consequence of the income inequality described above has detrimental psychoneuroendocrine effects (18). There is long-standing evidence that stress may be involved in at least some types of CVDs. For example, in the INTERHEART study, Rosengren et al. (29) found that psychosocial stressors were associated with a higher risk of acute MI. Chronic stress is associated with memory impairment, anxiety, and depression, all of which are common in HF and potentially harmful because of adverse effects on adherence and self-management (30,31). Moreover, recent evidence has suggested even more widespread biological consequences of stress including reduced immune responses and impaired endothelial function (32).

STUDY STRENGTHS AND LIMITATIONS. To the best of the present authors' knowledge, the current study is the first to investigate the association between income inequality and outcomes in HF (or any chronic disease) transnationally. However, the present study is based on a highly selected clinical trial population recruited from specific centers and may not necessarily represent the general population.

Not all the countries in this analysis were from similar income categories, and information on individual socioeconomic status was missing, but adjustment was made for per capita income representing population-level income for each country. Accordingly, differences in health care systems were not adjusted because most of the countries did not follow any particular health care system (33). An attempt was made to make up for those shortcomings to a certain degree by including information about hospital bed density and health worker density per 1,000 population. Patients were mandated by protocol to have been receiving ACE inhibitor (or ARB) therapy and beta-blocker therapy at the time of screening. There was also poor representation from Africa in the analysis (only patients from South Africa were included). A measurement that might have supported or refuted a "psychosocial" explanation for the association between greater income disparity and poor outcomes was lacking.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HF poses an enormous economic burden on society. It is the leading cause of hospitalization in Western countries and is steadily increasing in prevalence (and is especially concerning in younger people) in developing countries. In countries with prominent levels of income inequality, unfavorable social actors coupled with inadequate and inefficient public spending on health care may present considerable barriers not only to the prevention of CVD (the focus of most studies to date) but also to the improvement of outcomes in patients with established and chronic diseases such as HF.

TRANSLATIONAL OUTLOOK: If indeed income inequality does influence HF outcomes, both developing and developed nations need to consider how their public health policies can be modified to more effectively tackle this growing global epidemic.

REFERENCES

1. Callender T, Woodward M, Roth G, et al. Heart failure care in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med 2015;11:e1001699.

2. Kristensen SL, Martinez F, Jhund PS, et al. Geographic variations in the PARADIGM-HF heart failure trial. Eur Heart J 2016;37:3167–74.

3. Dokainish H, Teo K, Zhu J, et al. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Heal 2017;5:665–72.

4. Kawachi I, Kennedy BP. Income inequality and health: pathways and mechanisms. Health Serv Res 1999;34:215–27.

5. Kaplan GA, Pamuk ER, Lynch JW, Cohen RD, Balfour JL. Inequality in income and mortality in the United States: analysis of mortality and potential pathways. BMJ 1996;312:999–1003.

6. Rodgers GB. Income and inequality as determinants of mortality: an international cross-section analysis. Int J Epidemiol 2002;31:533–8.

7. Wilkinson RG. Income distribution and life expectancy. BMJ 1992;304:165–8.

8. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

9. McMurray JJV, Krum H, Abraham WT, et al. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. N Engl J Med 2016;374:1521–32.

10. United Nations. United Nations Development Programme. Income Gini Coefficient. Human Development Reports. 2013. Available at: http://hdr.undp.org/en/content/income-gini-coefficient. Accessed November 16, 2018.

11. Blakely TA, Kennedy BP, Glass R, Kawachi I. What is the lag time between income inequality and health status? J Epidemiol Community Health 2000;54:318–9.

12. The World Bank. GDP per Capita (Current US$). 2017. Available at: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD. Accessed November 16, 2018.

13. Central Intelligence Agency. FIELD LISTING: RELIGIONS. The World Fact Book. Washington, DC; 2017:1–119. Available at: https://www.cia.gov/library/publications/the-world-factbook/. Accessed November 16, 2018.

14. World Health Organization. Global Health Observatory Data Repository. Density per 1, 000; Data by Country. Geneva, Switzerland; WHO. Available at: http://apps.who.int/gho/data/node.main.A1444. Accessed November 16, 2018.

15. United Nations. United Nations Development Programme. Human Development Data (1980-2015). Human Development Reports. 2016. Available at: http://hdr.undp.org/en/data. Accessed November 16, 2018.

16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

17. Austin PC. A Tutorial on multilevel survival analysis: methods, models and applications. Int Stat Rev 2017;85:185–203.

18. Kim D, Kawachi I, Hoorn S Vander, Ezzati M. Is inequality at the heart of it? Cross-country associations of income inequality with cardiovascular diseases and risk factors. Soc Sci Med 2008;66:1719–32.

19. Kim D. The associations between US state and local social spending, income inequality, and individual all-cause and cause-specific mortality: the National Longitudinal Mortality Study. Prev Med (Baltimore) 2016;84:62–8.

20. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.

21. Kondo N, Sembajwe G, Kawachi I, Van Dam RM, Subramanian SV, Yamagata Z. Income inequality, mortality, and self rated health: meta-analysis of multilevel studies. BMJ 2009;339:1178–81.

22. Pickett KE, Wilkinson RG. Income inequality and health: a causal review. Soc Sci Med 2015;128:316–26.

23. López DB, Loehrer AP, Chang DC. Impact of Income Inequality on the Nation's Health. J Am Coll Surg 2016;223:587–94.

24. Devaux M. Income-related inequalities and inequities in health care services utilisation in 18 selected OECD countries. Eur J Health Econ 2015;16:21–33.

25. Carrieri V, Wuebker A. Assessing inequalities in preventive care use in Europe. Health Policy (New York) 2013;113:247–57.

26. Lindenauer PK, Lagu T, Rothberg MB, et al. Income inequality and 30 day outcomes after acute myocardial infarction, heart failure, and pneumonia: retrospective cohort study. BMJ 2013;346:f521.

27. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998;97:596–601.

28. Li H, Zhu Y. Income, income inequality, and health: evidence from China. J Comp Econ 2006;34:668–93.

29. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): case-control study. Lancet (London) 2004;364:953–62.

30. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. Am Heart J 2006;152:940.e1–8.

31. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure. a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48:1527–37.

32. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. J Psychosom Res 2002;52:1–23.

33. Physicians for a National Health Program. Health Care Systems-Four Basic Models. Chicago, IL: PNHP. Available at: http://www.pnhp.org/single_payer_resources/health_care_systems_four_basic_models.php. Accessed November 16, 2018.

KEY WORDS heart failure, income inequality

APPENDIX For an expanded methods section, supplemental figure and tables, and a list of PARADIGM-HF and ATMOSPHERE investigators, please see the online version of this paper.