Income level and inequality as complement to geographical differences in cardiovascular trials

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Background Analyses of country or regional differences in cardiovascular (CV) trials are based on geographical subgroup analyses. However, apart from map location and related racial, ethnic, and genetic variations, identified differences may also depend on social structure and provision and access to health care, for which country income and income inequality are indicators. The aim of the study was to examine the association between country per capita income and income inequality and prognosis in patients with heart failure or an acute coronary syndrome in 3 international trials (EMPHASIS-HF, EPHESUS, and EXAMINE).

Methods Countries were classified into high income or low-middle income (LMICs) and into low, middle, or high inequality using the Gini index. The main outcome measures were all-cause and CV death.

Results Patients from LMICs and countries with higher inequality were younger, were less often white, had fewer comorbid conditions, and were less often treated with guideline-recommended therapies, including devices. These patients had higher adjusted mortality rates (+15% to +70%) compared with patients from high-income countries and countries with less inequality. Patients from countries with the combination of greater inequality and low-middle income had particularly high mortality rates (+80% to +190%) compared with those that did not have both characteristics. Living in a country that is poor and has inequality had more impact on death rates than any comorbidity. These findings were reproduced in 3 trials.

Conclusions Patients from LMICs and countries with greater inequality had the highest mortality rates. The prognostic impact of income and inequality is substantial and should be considered when looking into subgroup differences in CV trials. (Am Heart J 2019;218:66-74.)

Event rates in cardiovascular (CV) trials have been falling progressively over the past 4 decades. To maintain statistical power, larger sample sizes are needed and more countries are now included, with more than 40 countries worldwide involved in many recent trials.[1,2] This large geographical footprint should increase the generalizability of the results of trials, although the rapid globalization of trials has also raised questions about differences in patient characteristics, in outcomes, and even in the effect of treatment between geographical areas.[3-5]

Most "geographical groupings" on which most subgroup analysis are performed are not supported (in most cases) by racial, social, health care, or medical practice grounds and are chosen solely based on the world-map location.[6,7] Instead of the map location, it can be argued that it makes more sense to categorize countries on the basis of health care and social provision, for which the country income (per capita) and wealth distribution are thought to be good surrogates.[8-10]

Income inequality has been associated with poorer health status and increased mortality in several populations.[11] We recently reported that income inequality, as assessed by the Gini coefficient, was associated with worse heart failure (HF) outcomes, with an impact similar to those of major comorbidities.[12] Moreover, poorer countries have shown slow or no progress in reducing the death rates attributable to noncommunicable diseases.[13] Whether income inequality and/or income per capita affect

death rates (including cause-specific death) and influence the treatment effect in CV trials is yet to be determined.

To further explore this alternative approach to grouping of countries, we examined patient characteristics, event rates (including cause-specific death), and potential heterogeneity of treatment effect in 3 large randomized trials in patients with HF or an acute coronary syndrome (ACS).

Methods

The trials analyzed in the present study are Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF)[14]; Eplerenone, a Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction (EPHESUS)[15]; and Alogliptin After Acute Coronary Syndrome in Patients With Type 2 Diabetes (EXAMINE).[16] The design, baseline characteristics, and results of these trials have been previously published.[14-16] The Ethics Committee of each of the participating institutions approved the respective protocols, and all patients gave written, informed consent.

Study patients

The entry criteria for these trials have been previously described in detail.[14-16] Briefly, in EMPHASIS-HF, 2,737 patients with HF in New York Heart Association class II and a left ventricular ejection fraction ≤35% were randomly assigned to eplerenone or placebo, in addition to recommended therapy.[14] In EPHESUS, 6,632 patients with acute myocardial infarction (MI) complicated by left ventricular systolic dysfunction and HF or diabetes were randomly assigned to eplerenone or placebo, in addition to recommended therapy.[15] In EXAMINE, 5,380 patients with type 2 diabetes and either an acute MI or unstable angina requiring hospitalization within the previous 15 to 90 days were randomly assigned to alogliptin or placebo in addition to existing glucose-lowering and CV drug therapy.[16]

Trial end points

For homogeneity reasons, the main end point considered for this analysis was all-cause death (CV death was also assessed). The primary end point was different in each of these trials and was considered as exploratory for the present analysis. The primary end point in EMPHASIS-HF was a composite of CV mortality or a first hospitalization for HF. The co-primary end point in the EPHESUS trial was a composite of CV hospitalization or CV death and all-cause death. The primary end point in the EXAMINE trial was a composite of CV death, nonfatal MI, or nonfatal stroke. All end points were independently adjudicated in each trial.

Countries income and inequality: distribution, classification, and correlation

The list of countries (and the respective Gini index and income) included in each of these trials is described in the Supplemental Tables I, II, and III.

The distribution and correlation of the Gini tertiles by income classification are depicted in the Supplemental Tables IV, V, and VI. Income and inequality were poorly correlated (<0.3 in all trials).

Income. Countries were grouped by the World Bank income classification (http://data.worldbank.org/about/country-and-lending-groups) into high-income and low-to middle-income countries (LMICs). The gross national income per capita (GNI) was calculated for each country using the World Bank method (https://datahelpdesk.worldbank.org/knowledgebase/articles/378832-what-is-the-world-bank-atlas-method). LMICs were those with a GNI inferior to \$12,476, and high-income countries were those with a GNI superior to \$12,476.

Inequality/wealth distribution/Gini index. The Gini index is a measure of statistical dispersion intended to represent the income or wealth distribution of a nation's residents and is the most commonly used measurement of inequality.[17] A Gini index of zero expresses perfect equality, whereas a Gini index of 1 (or 100%) expresses maximal inequality. The Gini index was calculated for each country using the World Bank data (https://data.worldbank.org/indicator/SI.POV.GINI) and the United Nations Development Programme (http://hdr.undp.org/en/content/income-gini-coefficient). Data from 2003 were used, whereby inequality up to 15 years previously may have a stronger association with health than current income inequality.[18] Because there is no "Gini threshold" for inequality, we divided this score in similarly distributed tertiles for each trial and expressed in percentage (%).

Statistical analysis

Data description is reported as mean ± SD and absolute numbers plus percentages for categorical variables. One-way t test and anaylsis of variance were used to compare baseline variables between income and Gini index tertiles. Cox proportional-hazard models were used to estimate hazard ratios (HRs) with 95% CIs for the time-to-event analyses. No violations of the proportional-hazards assumption were found on the basis of the scaled Schoenfeld residuals over time after fitting a Cox model. In the treatment effect analyses, a statistical interaction was tested between the allocated treatment (or placebo) and income or Gini index tertiles. The variables used for adjustment in the models have been associated with the prognosis in the studied trials[19,20]: EMPHASIS-HF: age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, diabetes, prior MI and/or coronary intervention, body mass index, hemoglobin, and prior hospitalization for HF; EPHESUS: age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, diabetes, prior MI and/or coronary intervention, body mass index, hemoglobin, and prior hospitalization for HF; EXAMINE: age, gender, systolic blood pressure, heart rate, estimated glomerular

Table I. EMPHASIS-HF: characteristics of the population by Gini coefficient tertiles and income

Gini tertiles/income	<28.3	28.3-34.3	>34.3	P value	High income	Low-middle income	P value
n	947	959	831		2107	630	
Age, y	69.3 ± 7.3	68.1 ± 7.6	68.4 ± 7.9	<.001	69.2 ± 7.8	66.9 ± 6.8	<.001
Male gender, n (%)	735 (77.6%)	754 (78.6%)	638 (76.8%)	.64	1656 (78.6%)	471 (74.8%)	.043
White race, n (%)	946 (99.9%)	725 (75.6%)	597 (71.8%)	<.001	1953 (92.7%)	315 (50.0%)	<.001
Low-middle income, n (%)	278 (29.4%)	202 (21.1%)	150 (18.1%)	<.001	–	–	–
Gini <28.3	–	–	–	–	669 (31.8%)	278 (44.1%)	<.001
28.3-34.3	–	–	–	–	757 (35.9%)	202 (32.1%)	
>34.3	–	–	–	–	681 (32.3%)	150 (23.8%)	
BMI, kg/m^2	28.1 ± 4.4	26.3 ± 4.8	28.1 ± 5.1	<.001	27.7 ± 4.7	26.8 ± 5.4	<.001
LVEF, %	26.8 ± 4.1	25.8 ± 4.8	25.6 ± 4.8	<.001	26.1 ± 4.8	26. ± 4.1	.44
SBP, mm Hg	127.4 ± 15.6	122.4 ± 17.71	122.2 ± 16.6	<.001	123.8 ± 16.9	125.1 ± 16.9	.085
Heart rate, beat/min	70.4 ± 12.1	72.8 ± 12.8	71.8 ± 12.2	<.001	71.1 ± 12.3	74.1 ± 12.6	<.001
eGFR, mL/min/1.73 m^2	75.2 ± 22.7	68.9 ± 21.0	67.7 ± 20.6	<.001	70.0 ± 21.3	73.3 ± 23.1	<.001
NYHA III/IV, n (%)	63 (6.6%)	97 (10.1%)	69 (8.3%)	<.001	196 (9.3%)	33 (5.2%)	<.001
Ischemic HF, n (%)	690 (72.9%)	631 (65.9%)	565 (68.2%)	.004	1382 (65.7%)	504 (80.4%)	<.001
Atrial fibrillation, n (%)	357 (37.7%)	247 (25.8%)	240 (28.9%)	<.001	721 (34.2%)	123 (19.5%)	<.001
Diabetes, n (%)	276 (29.1%)	318 (33.2%)	265 (31.9%)	.16	646 (30.7%)	213 (33.8%)	.13
Hypertension, n (%)	711 (75.1%)	552 (57.6%)	556 (66.9%)	<.001	1403 (66.6%)	416 (66.0%)	.80
Prior stroke, n (%)	107 (11.4%)	81 (8.5%)	74 (9.0%)	.085	203 (9.7%)	59 (9.5%)	.88
Cardiac device, n (%)	151 (16.2%)	215 (23.0%)	249 (30.6%)	<.001	597 (28.9%)	18 (2.9%)	<.001
PCI/CABG, n (%)	275 (29.0%)	354 (37.1%)	299 (36.0%)	<.001	823 (39.1%)	105 (16.7%)	<.001
ACE/ARB, n (%)	909 (96.0%)	885 (92.3%)	763 (91.8%)	<.001	1988 (94.4%)	569 (90.3%)	<.001
β-Blocker, n (%)	850 (90.2%)	804 (84.5%)	720 (87.0%)	<.001	1876 (89.5%)	498 (79.8%)	<.001
Lipid-lowering drug, n (%)	569 (60.4%)	651 (68.5%)	493 (59.5%)	<.001	1386 (66.1%)	327 (52.4%)	<.001
Digoxin, n (%)	230 (24.3%)	267 (27.8%)	243 (29.2%)	.050	524 (24.9%)	216 (34.3%)	<.001
Loop diuretics, n (%)	794 (84.3%)	830 (87.3%)	702 (84.8%)	.14	1773 (84.5%)	553 (88.6%)	.011

BMI, body mass index; *LVEF*, left ventricular ejection fraction; *SBP*, systolic blood pressure; *eGFR*, estimated glomerular filtration rate; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *ACEi*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker.

filtration rate, prior MI and/or coronary intervention, prior stroke, atrial fibrillation, body mass index, and prior hospitalization for HF. Moreover, in the analyses studying income, additional adjustment on Gini index was performed and vice versa. We also performed the analysis with models clustered on each country so that the standard errors allow for intragroup correlation (relaxing the usual requirement that the observations are independent); that is, the observations are independent across countries but not necessarily within countries, so that the income and Gini belong to a certain country. A 2-tailed *P* value < .05 was considered significant. Statistical analyses were performed using STATA (College Station, TX) version 15.0.

Results

The results of EMPHASIS-HF, EPHESUS, and EXAMINE according to income (LMIC vs high-income country) and Gini index tertiles are presented in Table I (EMPHASIS-HF) and Supplemental Tables VII (EPHESUS) and VIII (EXAMINE). Patients from areas with high inequality represented between 30% and 32% of the participants in all trials. Patients from LMICs represented 23% to 25% of the participants in the EMPHASIS-HF and EPHESUS trials, and 41% of the participants in the EXAMINE trial. Patients from LMICs and from countries with greater inequality were younger, were less often white, had fewer comorbid conditions, and were less often treated with guideline-recommended therapies, including devices (*P* < .05 for all).

Event rates

Patients from LMICs and from countries with greater inequality had higher adjusted mortality rates compared with patients from countries with high income and lower inequality (eg, adjusted HR [95% CI] for all-cause death in the EMPHASIS-HF trial =1.34 [1.03-1.74] for the highest Gini tertile and 1.70 [1.35-2.13] for LMICs). Similar results were found for CV death. The full results of each of EMPHASIS-HF, EPHESUS, and EXAMINE trials are shown in Tables II-IV, respectively. The association of the Gini index as a continuous variable and all-cause death is depicted in the Supplemental Figure 1. The association was "linear," with poorer outcomes for Gini index values above ±30%.

Patients from countries with the combination of low-middle income *and* greater inequality had particularly high mortality rates (eg, adjusted HR [95% CI] in the EMPHASIS-HF trial =2.38 [1.70-3.33] for Gini index ≥28.3 plus low-middle income compared with Gini index <28.3 plus high income as referent) (Tables II-IV). Similar observations were apparent for the primary outcome of each trial; however, no association between income alone and the primary outcome was found in the EPHESUS and EXAMINE trials (Tables II-IV).

Table II. EMPHASIS-HF: outcome associations by Gini coefficient tertiles and income.

Gini coefficient tertile	Incidence rate per 100 py	Crude HR (95% CI)	P value	Adjusted† HR (95% CI)	P value	Interaction P*
All-cause death						.75
Gini <28.3	6.4 (5.4-7.7)	Referent	–	Referent	–	–
Gini 28.3-34.3	10.1 (8.5-11.8)	1.52 (1.20-1.94)	.001	1.23 (0.95-1.58)	.11	–
Gini >34.3	10.0 (8.3-11.9)	1.57 (1.22-2.03)	.001	1.34 (1.03-1.74)	.030	–
CV death						.89
Gini <28.3	5.2 (4.3-6.3)	Referent	–	Referent	–	–
Gini 28.3-34.3	8.0 (6.7-9.5)	1.53 (1.18-1.98)	.001	1.32 (1.01-1.72)	.039	–
Gini >34.3	7.9 (6.5-9.6)	1.54 (1.17-2.03)	.002	1.31 (0.98-1.74)	.064	–
Primary outcome						.42
Gini <28.3	10.5 (9.1-12.1)	Referent	–	Referent	–	–
Gini 28.3-34.3	16.1 (14.2-18.3)	1.48 (1.23-1.79)	<.001	1.19 (0.98-1.46)	.076	–
Gini >34.3	15.0 (12.9-17.4)	1.36 (1.11-1.67)	.003	1.17 (0.94-1.44)	.15	–
Income category						
All-cause death						.38
High income	7.6 (6.7-8.6)	Referent	–	Referent	–	–
Low-middle income	11.7 (9.8-14.0)	1.73 (1.31-2.31)	<.001	1.70 (1.35-2.13)	<.001	–
CV death						.44
High income	5.9 (5.2-6.7)	Referent	–	Referent	–	–
Low-middle income	10.0 (8.3-12.1)	1.70 (1.35-2.14)	<.001	1.87 (1.47-2.37)	<.001	–
Primary outcome						.70
High income	12.7 (11.6-14.0)	Referent	–	Referent	–	–
Low-middle income	15.9 (13.6-18.5)	1.30 (1.03-1.64)	.027	1.33 (1.11-1.62)	.003	–
Gini-income combinations						
All-cause death						.75
Gini <28.3 & high income	6.3 (5.1-7.8)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	6.7 (4.9-9.2)	1.14 (0.78-1.67)	.67	1.45 (0.98-2.15)	.066	–
Gini ≥28.3 & high income	8.4 (7.2-9.7)	1.34 (1.03-1.75)	.028	1.23 (0.94-1.61)	.12	–
Gini ≥28.3 & low-middle income	18.0 (14.5-22.4)	2.92 (2.14-3.97)	<.001	2.38 (1.70-3.33)	<.001	–
CV death						.86
Gini <28.3 & high income	4.7 (3.7-6.0)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	6.4 (4.7-8.8)	1.37 (0.91-2.04)	.12	1.50 (1.00-2.26)	.049	–
Gini ≥28.3 & high income	6.6 (5.6-7.7)	1.42 (1.06-1.90)	.017	1.26 (0.94-1.70)	.12	–
Gini ≥28.3 & low-middle income	14.3 (11.4-18.1)	3.09 (2.21-4.33)	<.001	2.99 (2.08-4.29)	<.001	–
Primary outcome						.92
Gini <28.3 & high income	10.7 (9.1-12.7)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	9.9 (7.6-12.8)	0.93 (0.69-1.27)	.67	1.25 (0.91-1.72)	.17	–
Gini ≥28.3 & high income	13.9 (12.5-15.6)	1.26 (1.03-1.53)	.027	1.17 (0.95-1.44)	.13	–
Gini ≥28.3 & low-middle income	23.5 (19.5-28.4)	2.08 (1.62-2.69)	<.001	1.67 (1.27-2.19)	<.001	–

The primary outcome in EMPHASIS-HF was a composite of HF hospitalization or CV death.
* Eplerenone versus placebo by categories of Gini, income, and its combinations interaction.
† Model adjusted on age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, diabetes, prior MI and/or coronary intervention, body mass index, hemoglobin, and prior hospitalization for HF.

Living in a country that is poor and has inequality had more impact on death rates than any other comorbid condition (Figure 1).

No statistical heterogeneity (by income or inequality categories) was observed with regard to the treatment effect of the drugs studied in each of these trials for the outcomes of all-cause death and CV death (*P* for interaction > .05 for all trials) (Tables II-IV). However, in the EXAMINE trial, a statistically significant interaction was found with regard to the primary composite outcome, whereby alogliptin might have reduced the primary outcome event rates in patients from lower inequality areas (with a tendency for a beneficial effect in LMICs) (Supplemental Table 9).

The adjusted analyses using further correction for the participating countries as "clusters" provided similar results to those above described and are depicted in Supplemental Table X. The models adjusted on the % of the gross domestic product (GDP) spent on health care also provide very similar results to those presented. Income is highly correlated with % GDP spent on health care (Spearman ρ >0.7 for all trials) but not with Gini (Spearman ρ <0.3 for both % GDP spent on health care and income in all trials).

Discussion

The present analysis consistently shows that patients from LMICs and from countries with higher income inequality (ie, greater disparity in wealth distribution) were younger, were less often white, had fewer

Table III. EPHESUS: outcome associations by Gini coefficient tertiles and income.

Gini coefficient tertile	Incidence rate per 100 py	Crude HR (95% CI)	P value	Adjusted† HR (95% CI)	P value	Interaction P*
All-cause death						.75
Gini <28.3	9.8 (8.7-11.0)	Referent	–	Referent	–	–
Gini 28.3-34.3	12.8 (11.5-14.2)	1.29 (1.11-1.49)	.001	1.04 (0.89-1.21)	.61	–
Gini >34.3	13.7 (12.3-15.2)	1.34 (1.15-1.56)	<.001	1.26 (1.08-1.47)	.003	–
CV death						.42
Gini <28.3	8.6 (7.6-9.6)	Referent	–	Referent	–	–
Gini 28.3-34.3	11.1 (9.9-12.4)	1.28 (1.09-1.50)	.003	1.08 (0.92-1.27)	.36	–
Gini >34.3	11.6 (10.3-13.0)	1.30 (1.11-1.53)	.001	1.22 (1.04-1.44)	.017	–
Primary outcome						.18
Gini <28.3	21.3 (19.7-23.0)	Referent	–	Referent	–	–
Gini 28.3-34.3	27.5 (25.5-29.7)	1.27 (1.14-1.42)	<.001	1.08 (0.97-1.21)	.16	–
Gini >34.3	27.3 (25.2-29.6)	1.21 (1.08-1.36)	.001	1.15 (1.02-1.28)	.019	–
Income						
All-cause death						.26
High income	11.7 (10.9-12.6)	Referent	–	Referent	–	–
Low-middle income	12.6 (11.1-14.2)	1.14 (0.95-1.38)	.17	1.29 (1.12-1.49)	<.001	–
CV death						.34
High income	10.1 (9.3-10.9)	Referent	–	Referent	–	–
Low-middle income	10.9 (9.6-12.4)	1.08 (0.93-1.25)	.32	1.26 (1.08-1.47)	.003	–
Primary outcome						.30
High income	25.9 (24.7-27.4)	Referent	–	Referent	–	–
Low-middle income	22.2 (20.2-24.4)	0.91 (0.79-1.05)	.21	0.99 (0.89-1.11)	.98	–
Gini-income combinations						
All-cause death						.54
Gini <28.3 & high income	8.9 (7.7-10.4)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	11.1 (9.5-12.9)	1.24 (0.99-1.53)	.054	1.44 (1.16-1.79)	.001	–
Gini ≥28.3 & high income	12.8 (11.8-13.9)	1.41 (1.19-1.68)	<.001	1.29 (1.08-1.53)	.005	–
Gini ≥28.3 & low-middle income	16.0 (13.2-19.4)	1.73 (1.36-2.21)	<.001	1.82 (1.41-2.34)	<.001	–
CV death						.71
Gini <28.3 & high income	7.7 (6.5-9.0)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	9.7 (8.3-11.4)	1.26 (1.00-1.59)	.049	1.37 (1.08-1.73)	.008	–
Gini ≥28.3 & high income	11.0 (10.1-12.0)	1.41 (1.17-1.69)	<.001	1.27 (1.05-1.52)	.013	–
Gini ≥28.3 & low-middle income	13.5 (11.0-16.7)	1.69 (1.30-2.21)	<.001	1.79 (1.37-2.34)	<.001	–
Primary outcome						.51
Gini <28.3 & high income	23.2 (21.0-25.8)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	19.0 (16.8-21.5)	0.83 (0.71-0.97)	.021	0.92 (0.79-1.09)	.34	–
Gini ≥28.3 & high income	27.1 (25.5-28.7)	1.13 (1.01-1.28)	.039	1.05 (0.93-1.18)	.42	–
Gini ≥28.3 & low-middle income	29.9 (25.7-34.7)	1.22 (1.02-1.47)	.031	1.28 (1.06-1.54)	.010	–

The co-primary outcome in EPHESUS was a composite of CV hospitalization or CV death and all-cause death.
* Eplerenone versus placebo by categories of Gini, income, and its combinations interaction.
† Model adjusted on age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, diabetes, prior MI and/or coronary intervention, body mass index, hemoglobin, and prior hospitalization for HF.

comorbid conditions, and were less often treated with guideline-recommended therapies, especially devices. These patients had higher adjusted mortality rates compared with patients from high-income and lower-inequality areas, particularly when in countries with the combination of low-middle income and higher inequality. Importantly, living in countries with a low and unequally distributed wealth had a stronger association with death rate than any single comorbid condition. These findings were reproduced in the 3 trials including patients with HF or an ACS and are likely applicable to different patient populations. Although these findings may be applicable to the CV field, they are not exclusive of the CV field, as similar findings have been observed in multiple cohorts and populations,

including HF.[11,12] Notwithstanding, our findings expand the previous ones in several aspects: (1) we examined 2 distinct MI trial populations, one with systolic dysfunction (EPHESUS) and one with diabetes (EXAMINE), in addition to an HF trial population (EMPHASIS-HF); (2) we assessed the income inequality (Gini coefficient) and also the income per capita (based on World Bank data) for each country, and this allowed us to investigate the interplay between income (per capita) and inequality (Gini); (3) we report that the income level and inequality of income in respective countries were not well correlated, providing independent findings; and (4) in addition, we analyzed the interactions of the level of income and income inequality with the effects of the investigated treatments in the respective trials.

Table IV. EXAMINE: outcome associations by Gini coefficient tertiles and income.

Gini coefficient tertile	Incidence rate per 100 py	Crude HR (95% CI)	P value	Adjusted[†] HR (95% CI)	P value	Interaction P*[†]
All-cause death						.32
Gini <33.9	2.6 (2.1-3.3)	Referent	–	Referent	–	–
Gini 33.9-40.8	3.9 (3.2-4.8)	1.46 (1.10-1.96)	.009	1.58 (1.17-2.12)	.003	–
Gini >40.8	5.3 (4.5-6.2)	2.00 (1.53-2.61)	<.001	2.28 (1.73-2.99)	<.001	–
CV death						.35
Gini <33.9	1.8 (1.4-2.3)	Referent	–	Referent	–	–
Gini 33.9-40.8	2.0 (1.5-2.7)	1.08 (0.74-1.58)	.68	1.07 (0.73-1.57)	.72	–
Gini >40.8	3.4 (2.7-4.1)	1.84 (1.33-2.54)	<.001	2.17 (1.56-3.03)	<.001	–
Primary outcome						.004[‡]
Gini <33.9	6.4 (5.5-7.3)	Referent	–	Referent	–	–
Gini 33.9-40.8	9.6 (8.4-10.9)	1.47 (1.22-1.78)	<.001	1.49 (1.22-1.81)	<.001	–
Gini >40.8	7.8 (6.7-8.9)	1.20 (0.98-1.45)	.071	1.32 (1.08-1.61)	.006	–
Income						
All-cause death						.36
High income	3.1 (2.6-3.6)	Referent	–	Referent	–	–
Low-middle income	4.9 (4.2-5.6)	1.60 (1.29-1.99)	<.001	1.72 (1.37-2.17)	<.001	–
CV death						.96
High income	1.7 (1.36-2.10)	Referent	–	Referent	–	–
Low-middle income	3.3 (2.7-3.9)	1.96 (1.48-2.61)	<.001	2.17 (1.63-2.92)	<.001	–
Primary outcome						.036[‡]
High income	8.5 (7.7-9.4)	Referent	–	Referent	–	–
Low-middle income	6.7 (5.9-7.7)	0.81 (0.69-0.96)	.21	0.91 (0.77-1.07)	.27	–
Gini-income combinations						
All-cause death						.28
Gini <33.9 & high income	2.5 (1.9-3.3)	Referent	–	Referent	–	–
Gini <33.9 & low-middle income	2.8 (2.1-3.9)	1.13 (0.75-1.72)	.55	1.36 (0.88-2.09)	.16	–
Gini ≥33.9 & high income	3.5 (2.8-4.2)	1.36 (0.96-1.92)	.078	1.63 (1.15-2.31)	.007	–
Gini ≥33.9 & low-middle income	6.2 (5.3-7.4)	2.49 (1.79-3.47)	<.001	2.92 (2.09-4.10)	<.001	–
CV death						.51
Gini <33.9 & high income	1.4 (0.9-2.0)	Referent	–	Referent	–	–
Gini <33.9 & low-middle income	2.4 (1.7-3.4)	1.82 (1.09-3.02)	.021	2.03 (1.21-3.43)	.008	–
Gini ≥33.9 & high income	1.9 (1.5-2.5)	1.38 (0.87-2.20)	.17	1.51 (0.94-2.41)	.086	–
Gini ≥33.9 & low-middle income	3.8 (3.1-4.7)	2.82 (1.81-4.37)	<.001	3.34 (2.14-5.23)	<.001	–
Primary outcome						.002[‡]
Gini <33.9 & high income	8.1 (6.8-9.5)	Referent	–	Referent	–	–
Gini <33.9 & low-middle income	4.2 (3.3-5.5)	0.54 (0.40-0.73)	<.001	0.64 (0.47-0.87)	.005	–
Gini ≥33.9 & high income	8.8 (7.7-9.9)	1.07 (0.87-1.32)	.51	1.18 (0.95-1.46)	.13	–
Gini ≥33.9 & low-middle income	8.4 (7.3-9.7)	1.05 (0.84-1.31)	.66	1.23 (0.98-1.54)	.071	–

The primary outcome in EXAMINE was a composite of CV death, nonfatal MI, or nonfatal stroke.
* Alogliptin versus placebo by categories of Gini, income, and its combinations interaction.
† Model adjusted on age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, prior MI and/or coronary intervention, prior stroke, atrial fibrillation, body mass index, and prior hospitalization for HF.
‡ Please see the Supplemental Table 9 for interaction details.

Country income and wealth distribution may have major impact on the provision of, availability, accessibility to, affordability, and acceptability of life-saving therapies, and also on nutrition, education, employment, provision of health care, and social support, all factors that have major influence on the outcomes of CV diseases.[8,9,21,22] Of note, approximately 80% of the more than 17 million deaths annually worldwide from CV causes occur in LMICs, and improving CV outcomes in these countries is a major challenge for the 21st century.[18-21] Moreover, countries sharing the same GDP may have different health outcomes, reflecting the distribution of income within those societies.[23] Even within a single country, the income inequality may have

impact in life expectancy, with greater longevity observed in higher-income groups.[24] In our study, patients from higher-income areas were more symptomatic, had more comorbid conditions (possibly also due to a more accurate diagnosis and treatment, as, for example, in the case of MI and atrial fibrillation), and despite this, they lived longer. On the other hand and similarly to epidemiological studies, we found that patients enrolled in LMICs and in areas with higher inequality in wealth distribution were younger and had fewer comorbidities, were less often treated with guideline-recommended therapies, and had higher mortality rates.[25] We cannot ascertain whether the higher mortality rates (including CV death) observed in the areas that are poorer and had more inequality were due to

Figure 1

A) EMPHASIS-HF

B) EPHESUS

C) EXAMINE
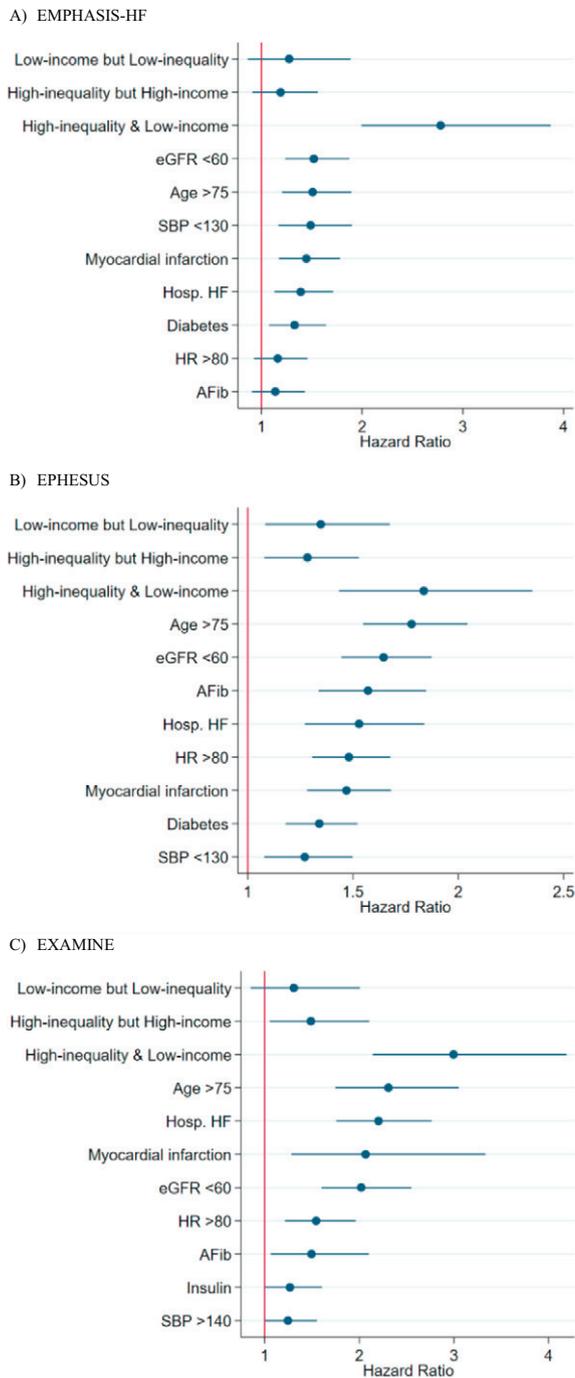
Comparison of the HRs and respective 95% CIs for Gini-income combinations with other common risk factors for the outcome of all-cause death. *SBP*, systolic blood pressure; *eGFR*, estimated glomerular filtration rate; *HR*, heart rate; *AFib*, atrial fibrillation. The referent variable (with the best prognostic associations) for the Gini-income combinations is low inequality and high income.

lower utilization of life-saving therapies, more limited access to health and social care, or some combination of these and perhaps other factors.[26-28] Moreover, given the "clinical trial setting," in many LMICs (which have high out-of-pocket costs), participation in trials is often the only opportunity to have access to medical care. This creates a potential ethical dilemma, where patients are forced into clinical trials out of deprivation. Moreover, the resulting medical products following a positive trial will often be out of reach for the trial patients after trial termination. This might also provide for a potential explanation for the differences in representativeness of trial populations across regions.[29] Our findings, supporting many other epidemiological studies examining a range of CV diseases, reinforce the need to improve health and social care in lower-income countries and in high-income countries where wealth disparities are marked.

This is particularly important because we found that the effects of treatment were generally homogeneous across country income categories and Gini index tertiles; that is, people in societies with limited wealth or large disparities in wealth distribution have as much to gain from therapies that they may not have access to.[30] Notwithstanding, potential heterogeneity (with a statistically significant interaction) might have been found with alogliptin in the EXAMINE trial, whereby this SGLT2-inhibitor might have reduced the primary composite outcome of CV death, MI, or stroke in patients from lower-inequality areas (with a tendency for a beneficial effect in LMICs). It should be highlighted that these findings may be due to chance, were not prespecified, and were not corrected for multiplicity of tests and that the trial lacks power to assess the treatment effects in subgroups. Therefore, these data should be interpreted with caution. It has been nonetheless hypothesized that patients from low-income areas may sometimes benefit more from a new "add-on" treatment because they are less often treated with updated guideline-oriented background therapy.[30] Furthermore, the presence of heterogeneity (ie, statistical interaction between subgroups) within a trial may limit the internal validity of a given trial and, in consequence, limit the generalization of the results to other populations.[31] The need for high and fast enrollment rates in trials, while cutting costs, may lead to an increasing enrollment of patients from LMICs, which may limit the generalizability of the results to higher-income areas. For example, is alogliptin effective in patients with less background therapy or was it just a "chance" finding? Although this is a hypothesis-generating post hoc analysis, these data can be used for designing better future trials (eg, balance enrollment throughout the world areas based on income).[29]

Income and wealth distribution have a weaker association with the primary outcome of these trials than with all-cause death. The primary outcome was different between the studied trials but always included a composite of a nonfatal event(s) plus a cause-specific fatal event (CV

death). The utilization of composite outcomes became routine in contemporary trials[32]; however, biases are potentially more important in assessment of nonfatal outcomes and include event underreporting, lower event rates due to limited access to health care facilities in lower-income countries, and difficulties in adjudication due to lower levels of investigation and treatment (eg, absence of advanced imaging and procedural treatments in lower-income countries and countries with high income inequality).[33] Enrolling a high proportion of patients from lower-income countries may thus affect the distribution of events in the primary composite outcome of trials. Hence, trialists and industry have also an opportunity to identify disparities in patient care and identify gaps in health care delivery in LMICs and in countries with high wealth disparity. This information can contribute to the evidence highlighting the need to reduce these important asymmetries between and within countries, and hopefully, trials can also be used to demonstrate narrowing of these disparities over time. Less importantly, these findings also emphasize the need for cost-effectiveness analyses to be conducted in a range of economic settings, although they also show that the overall, global effect of treatment is applicable in individual economic environments.

Limitations

Several limitations should be noted. First, this is a secondary nonprespecified analysis; hence, the limitations inherent to observational studies apply herein. Second, we studied 3 large clinical trials; therefore, the studied patient population is selected according to entry criteria in the respective trials. This selected population was motivated to participate in clinical research, attends to hospitals with research capacity (including a research team with doctors and nurses), and may have easier access to the health care facilities; therefore, these results may not apply to the overall population of the respective regions with the studied conditions. Third, our income and wealth distribution categories may not provide a precise reflection of the social and health care characteristics of the respective countries. Fourth, the majority of the countries participating in clinical trials are high-income or upper-middle–income ones; therefore, these data cannot be generalized to the great majority of the low-income countries (which were excluded from these trials). Notwithstanding, this provides an opportunity for the inclusion of more low-income countries in trials and clinical research in general. Fifth, we used "unsupervised tertiles" to illustrate the associations of the Gini coefficient in the outcomes. In a previous study,[11] the authors suggested that a Gini cutoff ≥30% may provide stronger associations with adverse outcomes. The tertile cutoffs above which mortality was higher in these trials were close to that suggested 30% cut point (28.3% in EMPHASIS-HF and EPHESUS, and 33.9% in EXAMINE). Hence, applying the 30% cut point in the present study would provide similar results to those presented (as also illustrated in the Supplemental Figure 1). Sixth, the primary outcome varied across the studied trials and may reflect other aspects of health and social care, such as accessibility, affordability, and event adjudication. Therefore, all-cause death is the only reproducible measure across countries and trials. Lastly, data from 2003 were used to take into account the "lag effect" (as described in the "Methods" section). This approach may be limited given the different periods on which these trials were performed (from 1999 to 2013). However, these indexes remain quite stable in 10- to 15-year periods and may provide a good compromise for these analyses.

Conclusions

Patients from LMICs and countries with higher income inequality had higher mortality rates compared to patients from high-income and low-inequality areas. The prognostic impact of income and inequality is clinically important and should be considered when assessing geographical differences in CV trials beyond "arbitrary" geographical subgroups based on the world-map location.

Disclosures

The clinical trial sponsor was not involved in the analysis, interpretation of data, writing of the report, or the decision to publish. The authors have no conflicts of interest to declare with regard to the present study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.08.019.

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