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Income Level and Inequality as complement to Geographical Differences in Cardiovascular trials

João Pedro Ferreira, MD, PhD^{1,2}; Patrick Rossignol, MD, PhD¹; Pooja Dewan MB ChB³; Zohra Lamiral, Msc¹; William B. White, MD⁴, PhD; Bertram Pitt, MD⁵; John J.V. McMurray, MD, PhD³; Faiez Zannad, MD, PhD¹

¹Université de Lorraine, Inserm, Centre d'Investigation Clinique Plurithématique 1433, U1116, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France ; ²Department of Physiology and Cardiothoracic Surgery, Cardiovascular Research and Development Unit, Faculty of Medicine, University of Porto, Porto, Portugal; ³Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; ⁴Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, CT 06032, USA; ⁵University of Michigan School of Medicine, Ann Arbor, Michigan.

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Correspondance to:

Professor Faiez Zannad: f.zannad@chru-nancy.fr

Centre d'Investigation Clinique Plurithématique1433

CHRU Nancy - Hôpitaux de Brabois

Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu

4 rue du Morvan, 54500 Vandoeuvre-lès-Nancy

Tel : +33 03 83 15 73 15

Fax : +33 03 83 15 73 24

Abstract

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.

Aims: To study the association between country per capita income and income-inequality and prognosis in patients with heart failure (HF) or an acute coronary syndrome (ACS) in three international trials (EMPHASIS-HF, EPHEBUS, and EXAMINE).

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

Results: Patients from LMICs and countries with higher inequality were younger, less often white, had fewer co-morbid 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 poor and inequal country had more impact on death rates than any co-morbidity. These findings were reproduced in 3 trials.

Conclusion: 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 cardiovascular trials.

Key-words: geographical differences; income; inequality; cardiovascular trials

Introduction

Event rates in cardiovascular (CV) trials have been falling progressively over the past four 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, outcomes and even in the effect of treatment between geographical areas³⁻⁵.

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 surrogates⁸⁻¹⁰.

Income inequality has been associated with poorer health status and increased mortality in several populations¹¹. We recently reported that income-inequality, as assessed by the Gini coefficient, was associated with worse heart failure outcomes, with an impact similar to those of major co-morbidities¹². Moreover, poorer countries have shown slow or no progress in reducing the death rates attributable to non-communicable diseases¹³. 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 three large randomized trials in patients with heart failure (HF) or an acute coronary syndrome (ACS).

Methods

The trials analyzed in the present study are: EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms)¹⁴, EPHESUS (Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction)¹⁵, and EXAMINE (Alogliptin after acute coronary syndrome in patients with type 2 diabetes)¹⁶. The design, baseline characteristics and results of these trials have been previously published¹⁴⁻¹⁶. 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 detail¹⁴⁻¹⁶. Briefly, in EMPHASIS-HF 2,737 patients with HF in NYHA class II and a left ventricular ejection fraction $\leq 35\%$ were randomly assigned to eplerenone or placebo, in addition to recommended therapy¹⁴.

In EPHEBUS 6,632 patients with acute MI complicated by left ventricular systolic dysfunction and HF or diabetes were randomly assigned to eplerenone or placebo, in addition to recommended therapy¹⁵. 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 cardiovascular drug therapy¹⁶.

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 EPHEBUS 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 1, 2 & 3**.

The distribution and correlation of the Gini tertiles by income classification is depicted in the **Supplemental Tables 4, 5 & 6**. 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>) in high income and low-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>). Low and middle-income countries (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 inequality¹⁷. 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-inequality¹⁸. 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 \pm standard deviation and absolute numbers plus percentages for categorical variables. One-way t-test and ANOVA were used to compare baseline variables between income and Gini index tertiles. Cox proportional hazard models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) 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 myocardial infarction and/or coronary intervention, body mass index, hemoglobin and prior hospitalization for heart failure; EPHEUS: age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, diabetes, prior myocardial infarction and/or coronary intervention, body mass index, hemoglobin and prior hospitalization for heart failure; EXAMINE: age, gender, systolic blood pressure, heart rate, estimated glomerular filtration rate, prior myocardial infarction and/or coronary intervention, prior stroke, atrial fibrillation, body mass index, and prior hospitalization for heart failure. 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) i.e. the observations are independent across countries but not necessarily within countries, so that the income/Gini belong to a certain country. A 2-tailed P-value <0.05 was considered significant. Statistical analyses were performed using STATA, College Station, Texas, version 15.0.

Results

The results of EMPHASIS-HF, EPHEUS and EXAMINE according to income (LMIC vs. high-income) and Gini index tertiles are presented in the **Table 1** (EMPHASIS-HF) and **Supplemental Tables 7** (EPHEUS) & **8** (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 EPHEUS trials, and 41% of the participants in the EXAMINE trial. Patients from LMICs and from countries with greater inequality were younger, less often white, had fewer co-morbid conditions, and were less often treated with guideline-recommended therapies, including devices ($p<0.05$ for all).

Event rates

Patients from LMICs and from countries with greater inequality had higher adjusted mortality rates compared with patients from high-income and lower inequality areas (e.g. 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, EPHEBUS and EXAMINE trials are shown in the **Tables 2, 3 & 4**, 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 $\pm 30\%$.

Patients from countries with the combination of low-middle income *and* greater inequality had particularly high mortality rates (e.g. 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) - see **Tables 2, 3 & 4**. 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 EPHEBUS and EXAMINE trials. **Tables 2, 3 & 4**.

Living in a poor and inequal country had more impact on death rates than any other co-morbid condition. **Figure 1**.

No statistical heterogeneity (by income or inequality categories) was observed with regards 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 > 0.05 for all trials) – see **Tables 2, 3 & 4**. However, in the EXAMINE trial a statistically significant interaction was found with regards 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 low-middle income countries). **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 the **Supplemental Table 10**. 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 Rho > 0.7 for all trials), but not with Gini (Spearman Rho < 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 (i.e. greater disparity in wealth distribution) were younger, less often white, had fewer co-morbid 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 co-morbid condition. These findings were reproduced in the 3 trials including patients with HF or an acute coronary syndrome and is likely applicable to different patient-populations. As 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 two distinct myocardial infarction trial populations, one with systolic dysfunction (EPHESUS), and one with diabetes (EXAMINE), in addition to a heart failure 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.

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 twenty-first century¹⁸⁻²¹. Moreover, countries sharing the same gross domestic product may have different health outcomes, reflecting the distribution of income within those societies²³. Even within a single country, the income inequality may have impact in life expectancy, with greater longevity observed in higher income groups²⁴. In our study patients from higher income areas were more symptomatic, had more co-morbid conditions (possibly also due to a more accurate diagnosis and treatment, as, for example, in the case of myocardial infarction 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 co-morbidities, were less often treated with guideline-recommended therapies and had higher mortality rates²⁵. We cannot ascertain whether the higher mortality rates (including CV death) observed in the poorer and more unequal areas was due to lower utilization of life-saving therapies, more limited access to health and social care, or to some combination of these and perhaps other factors²⁶⁻²⁸. 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 regions²⁹. 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 as we found the effects of treatment were generally homogeneous across country income categories and Gini index tertiles i.e., showing 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 to³⁰. 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 low-middle income countries). It should be highlighted that these findings may be due to chance, were not prespecified, not corrected for multiplicity of tests and 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 therapy³⁰. Furthermore, the presence of heterogeneity (i.e. 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 populations³¹. 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? While this is a hypothesis-generating post-hoc analysis, these data can be used for better designing future trials (e.g. 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 non-fatal event(s) plus a cause-specific fatal event (CV death). The utilization of composite outcomes became routine in contemporary trials³², however biases are potentially more important in assessment of non-fatal 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 (e.g., absence of advanced imaging and procedural treatments in lower income countries and countries with high income inequality)³³. Enrolling 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 LMIC 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 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 non-prespecified 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 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 study¹¹, the authors suggested that a Gini cutoff $\geq 30\%$ 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 EPHEBUS, 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.

Conclusion

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 cardiovascular trials beyond “arbitrary” geographical subgroups based on the world map location.

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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 regards to the present study.

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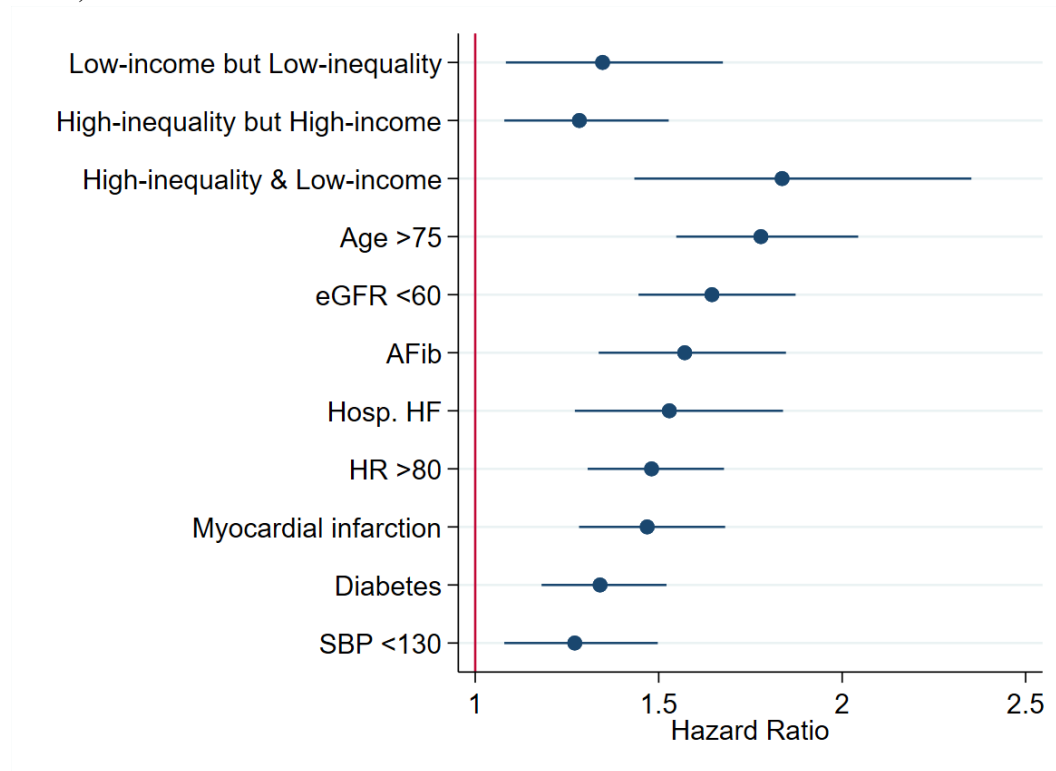
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Figure 1. Comparison of the Hazard Ratios and respective 95% CIs for Gini-income combinations with other common risk factors for the outcome of all-cause death

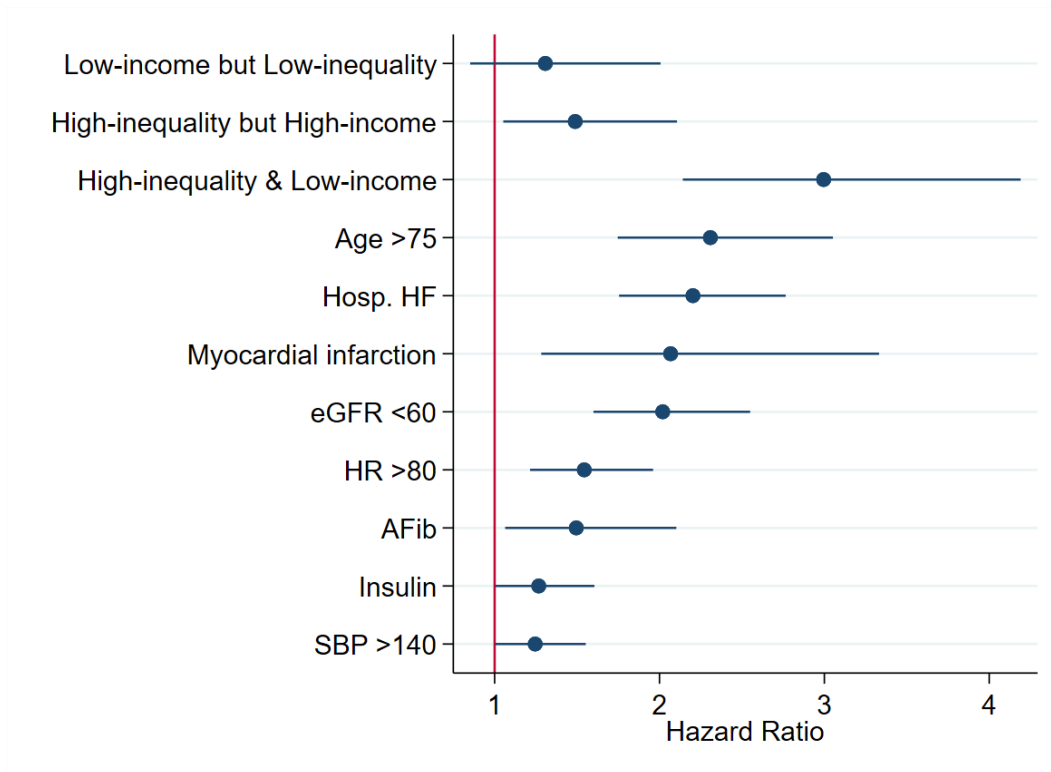
A) EMPHASIS-HF



B) EPHEBUS



C) EXAMINE



Legend: SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; HR, heart rate; AFib, atrial fibrillation.

The referent variable (with the best prognostic associations) for the Gini-income combinations is Low-inequality & High-income.

Table 1. 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, years	69.3±7.3	68.1±7.6	68.4±7.9	<0.001	69.2±7.8	66.9±6.8	<0.001
Male gender, n (%)	735 (77.6%)	754 (78.6%)	638 (76.8%)	0.64	1656 (78.6%)	471 (74.8%)	0.043
White race, n (%)	946 (99.9%)	725 (75.6%)	597 (71.8%)	<0.001	1953 (92.7%)	315 (50.0%)	<0.001
Low-Middle income, n (%)	278 (29.4%)	202 (21.1%)	150 (18.1%)	<0.001	-	-	-
Gini <28.3	-	-	-	-	669 (31.8%)	278 (44.1%)	<0.001
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	<0.001	27.7±4.7	26.8±5.4	<0.001
LVEF, %	26.8±4.1	25.8±4.8	25.6±4.8	<0.001	26.1±4.8	26.±4.1	0.44
SBP, mmHg	127.4±15.6	122.4±17.71	122.2±16.6	<0.001	123.8±16.9	125.1±16.9	0.085
Heart rate, bpm	70.4±12.1	72.8±12.8	71.8±12.2	<0.001	71.1±12.3	74.1±12.6	<0.001
eGFR, ml/min/1.73m ²	75.2±22.7	68.9±21.0	67.7±20.6	<0.001	70.0±21.3	73.3±23.1	<0.001
NYHA III/IV, n (%)	63 (6.6%)	97 (10.1%)	69 (8.3%)	<0.001	196 (9.3%)	33 (5.2%)	<0.001
Ischemic HF, n (%)	690 (72.9%)	631 (65.9%)	565 (68.2%)	0.004	1382 (65.7%)	504 (80.4%)	<0.001
Atrial fibrillation, n (%)	357 (37.7%)	247 (25.8%)	240 (28.9%)	<0.001	721 (34.2%)	123 (19.5%)	<0.001
Diabetes, n (%)	276 (29.1%)	318 (33.2%)	265 (31.9%)	0.16	646 (30.7%)	213 (33.8%)	0.13
Hypertension, n (%)	711 (75.1%)	552 (57.6%)	556 (66.9%)	<0.001	1403 (66.6%)	416 (66.0%)	0.80
Prior stroke, n (%)	107 (11.4%)	81 (8.5%)	74 (9.0%)	0.085	203 (9.7%)	59 (9.5%)	0.88
Cardiac device, n (%)	151 (16.2%)	215 (23.0%)	249 (30.6%)	<0.001	597 (28.9%)	18 (2.9%)	<0.001
PCI/CABG, n (%)	275 (29.0%)	354 (37.1%)	299 (36.0%)	<0.001	823 (39.1%)	105 (16.7%)	<0.001
ACE/ARB, n (%)	909 (96.0%)	885 (92.3%)	763 (91.8%)	<0.001	1988 (94.4%)	569 (90.3%)	<0.001
Beta-blocker, n (%)	850 (90.2%)	804 (84.5%)	720 (87.0%)	<0.001	1876 (89.5%)	498 (79.8%)	<0.001
Lipid-lowering drug, n (%)	569 (60.4%)	651 (68.5%)	493 (59.5%)	<0.001	1386 (66.1%)	327 (52.4%)	<0.001
Digoxin, n (%)	230 (24.3%)	267 (27.8%)	243 (29.2%)	0.050	524 (24.9%)	216 (34.3%)	<0.001
Loop diuretics, n (%)	794 (84.3%)	830 (87.3%)	702 (84.8%)	0.14	1773 (84.5%)	553 (88.6%)	0.011

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

Table 2. EMPHASIS-HF: outcome associations by Gini coefficient tertiles and income

Gini coefficient tertile	Incidence rate per 100py	Crude HR (95% CI)	P-value	Adjusted** HR (95% CI)	P-value	Interaction P*
<i>All-cause death</i>						0.75
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)	0.001	1.23 (0.95-1.58)	0.11	-
Gini >34.3	10.0 (8.3-11.9)	1.57 (1.22-2.03)	0.001	1.34 (1.03-1.74)	0.030	-
<i>CV death</i>						0.89
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)	0.001	1.32 (1.01-1.72)	0.039	-
Gini >34.3	7.9 (6.5-9.6)	1.54 (1.17-2.03)	0.002	1.31 (0.98-1.74)	0.064	-
<i>Primary outcome</i>						0.42
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)	<0.001	1.19 (0.98-1.46)	0.076	-
Gini >34.3	15.0 (12.9-17.4)	1.36 (1.11-1.67)	0.003	1.17 (0.94-1.44)	0.15	-
Income category						
<i>All-cause death</i>						0.38
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)	<0.001	1.70 (1.35-2.13)	<0.001	-
<i>CV death</i>						0.44
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)	<0.001	1.87 (1.47-2.37)	<0.001	-

Primary outcome						0.70
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)	0.027	1.33 (1.11-1.62)	0.003	-
Gini-Income combinations						
All-cause death						0.75
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)	0.67	1.45 (0.98-2.15)	0.066	-
Gini ≥28.3 & High-income	8.4 (7.2-9.7)	1.34 (1.03-1.75)	0.028	1.23 (0.94-1.61)	0.12	-
Gini ≥28.3 & Low-Middle income	18.0 (14.5-22.4)	2.92 (2.14-3.97)	<0.001	2.38 (1.70-3.33)	<0.001	-
CV death						0.86
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)	0.12	1.50 (1.00-2.26)	0.049	-
Gini ≥28.3 & High-income	6.6 (5.6-7.7)	1.42 (1.06-1.90)	0.017	1.26 (0.94-1.70)	0.12	-
Gini ≥28.3 & Low-Middle income	14.3 (11.4-18.1)	3.09 (2.21-4.33)	<0.001	2.99 (2.08-4.29)	<0.001	-
Primary outcome						0.92
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)	0.67	1.25 (0.91-1.72)	0.17	-
Gini ≥28.3 & High-income	13.9 (12.5-15.6)	1.26 (1.03-1.53)	0.027	1.17 (0.95-1.44)	0.13	-
Gini ≥28.3 & Low-Middle income	23.5 (19.5-28.4)	2.08 (1.62-2.69)	<0.001	1.67 (1.27-2.19)	<0.001	-

*Eplerenone vs. 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 myocardial infarction and/or coronary intervention, body mass index, hemoglobin and prior hospitalization for heart failure.

The primary outcome in EMPHASIS-HF was a composite of heart failure hospitalization or cardiovascular death

Table 3. EPHEBUS: outcome associations by Gini coefficient tertiles and income

Gini coefficient tertile	Incidence rate per 100py	Crude HR (95% CI)	p-value	Adjusted** HR (95% CI)	p-value	Interaction P*
<i>All-cause death</i>						0.75
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)	0.001	1.04 (0.89-1.21)	0.61	-
Gini >34.3	13.7 (12.3-15.2)	1.34 (1.15-1.56)	<0.001	1.26 (1.08-1.47)	0.003	-
<i>CV death</i>						0.42
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)	0.003	1.08 (0.92-1.27)	0.36	-
Gini >34.3	11.6 (10.3-13.0)	1.30 (1.11-1.53)	0.001	1.22 (1.04-1.44)	0.017	-
<i>Primary outcome</i>						0.18
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)	<0.001	1.08 (0.97-1.21)	0.16	-
Gini >34.3	27.3 (25.2-29.6)	1.21 (1.08-1.36)	0.001	1.15 (1.02-1.28)	0.019	-
Income						
<i>All-cause death</i>						0.26
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)	0.17	1.29 (1.12-1.49)	<0.001	-
<i>CV death</i>						0.34
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)	0.32	1.26 (1.08-1.47)	0.003	-

Primary outcome						0.30
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)	0.21	0.99 (0.89-1.11)	0.98	-
Gini-Income combinations						
All-cause death						0.54
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)	0.054	1.44 (1.16-1.79)	0.001	-
Gini ≥28.3 & High-income	12.8 (11.8-13.9)	1.41 (1.19-1.68)	<0.001	1.29 (1.08-1.53)	0.005	-
Gini ≥28.3 & Low-Middle income	16.0 (13.2-19.4)	1.73 (1.36-2.21)	<0.001	1.82 (1.41-2.34)	<0.001	-
CV death						0.71
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)	0.049	1.37 (1.08-1.73)	0.008	-
Gini ≥28.3 & High-income	11.0 (10.1-12.0)	1.41 (1.17-1.69)	<0.001	1.27 (1.05-1.52)	0.013	-
Gini ≥28.3 & Low-Middle income	13.5 (11.0-16.7)	1.69 (1.30-2.21)	<0.001	1.79 (1.37-2.34)	<0.001	-
Primary outcome						0.51
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)	0.021	0.92 (0.79-1.09)	0.34	-
Gini ≥28.3 & High-income	27.1 (25.5-28.7)	1.13 (1.01-1.28)	0.039	1.05 (0.93-1.18)	0.42	-
Gini ≥28.3 & Low-Middle income	29.9 (25.7-34.7)	1.22 (1.02-1.47)	0.031	1.28 (1.06-1.54)	0.010	-

*Eplerenone vs. 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 myocardial infarction and/or coronary intervention, body mass index, hemoglobin and prior hospitalization for heart failure.

The co-primary outcome in EPHEsus was a composite of cardiovascular hospitalization or cardiovascular death and all-cause death.

Table 4. EXAMINE: outcome associations by Gini coefficient tertiles and income

Gini coefficient tertile	Incidence rate per 100py	Crude HR (95% CI)	p-value	Adjusted** HR (95% CI)	p-value	Interaction P*
<i>All-cause death</i>						0.32
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)	0.009	1.58 (1.17-2.12)	0.003	-
Gini >40.8	5.3 (4.5-6.2)	2.00 (1.53-2.61)	<0.001	2.28 (1.73-2.99)	<0.001	-
<i>CV death</i>						0.35
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)	0.68	1.07 (0.73-1.57)	0.72	-
Gini >40.8	3.4 (2.7-4.1)	1.84 (1.33-2.54)	<0.001	2.17 (1.56-3.03)	<0.001	-
<i>Primary outcome</i>						0.004***
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)	<0.001	1.49 (1.22-1.81)	<0.001	-
Gini >40.8	7.8 (6.7-8.9)	1.20 (0.98-1.45)	0.071	1.32 (1.08-1.61)	0.006	-
Income						
<i>All-cause death</i>						0.36
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)	<0.001	1.72 (1.37-2.17)	<0.001	-
<i>CV death</i>						0.96
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)	<0.001	2.17 (1.63-2.92)	<0.001	-

Primary outcome						0.036***
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)	0.21	0.91 (0.77-1.07)	0.27	-
Gini-Income combinations						
All-cause death						0.28
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)	0.55	1.36 (0.88-2.09)	0.16	-
Gini ≥33.9 & High-income	3.5 (2.8-4.2)	1.36 (0.96-1.92)	0.078	1.63 (1.15-2.31)	0.007	-
Gini ≥33.9 & Low-Middle income	6.2 (5.3-7.4)	2.49 (1.79-3.47)	<0.001	2.92 (2.09-4.10)	<0.001	-
CV death						0.51
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)	0.021	2.03 (1.21-3.43)	0.008	-
Gini ≥33.9 & High-income	1.9 (1.5-2.5)	1.38 (0.87-2.20)	0.17	1.51 (0.94-2.41)	0.086	-
Gini ≥33.9 & Low-Middle income	3.8 (3.1-4.7)	2.82 (1.81-4.37)	<0.001	3.34 (2.14-5.23)	<0.001	-
Primary outcome						0.002***
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)	<0.001	0.64 (0.47-0.87)	0.005	-
Gini ≥33.9 & High-income	8.8 (7.7-9.9)	1.07 (0.87-1.32)	0.51	1.18 (0.95-1.46)	0.13	-
Gini ≥33.9 & Low-Middle income	8.4 (7.3-9.7)	1.05 (0.84-1.31)	0.66	1.23 (0.98-1.54)	0.071	-

*Alogliptin vs. 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 myocardial infarction and/or coronary intervention, prior stroke, atrial fibrillation, body mass index, and prior hospitalization for heart failure.

***Please see the Supplemental Table 9 for interaction details.

The primary outcome in EXAMINE was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.