Global Disparities in the Prescription of Guideline-Recommended Medical Therapies for Heart Failure with Reduced Ejection Fraction: A Cohort Study

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Abstract

Background. Heart failure (HF) is a global challenge, with lower- and middle-income countries carrying a large share of the burden. Treatment for HF with reduced ejection fraction (HFrEF) improves survival but is often underused. Economic factors might have an important effect on the use of medicines.

Methods and results This analysis assessed prescription rates and doses of renin-angiotensin-system (RAS) inhibitors, β-blockers, and mineralocorticoid receptor antagonists at discharge and 6-month follow-up in 8669 patients with HFrEF (1,458 from low-, 3,363 from middle- and 3,848 from high-income countries) hospitalized for acute HF in 44 countries in the prospective REPORT-HF study. We investigated determinants of guideline-recommended treatments and their association with 1-year mortality, correcting for treatment indication bias.

Only 37% of patients at discharge and 34% of survivors at six months were on all three medication classes, with lower proportions in low- or middle-income countries than high-income countries (19% vs. 41% at discharge and 15% vs. 39% at six months). Women and patients without health insurance, or from low- or middle-income countries, or without a scheduled medical follow-up within 6 months of discharge were least likely to be on guideline-recommended therapy at target doses, independent of confounders. Being on ≥50% of guideline-recommended doses of RAS-inhibitors, and β-blockers was independently associated with better 1-year survival, regardless of country income level.

Conclusion. Patients with HFrEF in low- and middle-income countries are less likely to receive guideline-recommended therapy at target-doses. Improved access to medications and medical care could reduce international disparities in outcome.

Trial registration: NCT02595814

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Abbreviations

ACEi, angiotensin-converting enzyme inhibitor

AHF, acute heart failure

ARB, angiotensin II receptor blocker

ARNi, angiotensin receptor neprilysin inhibitor

CABG, coronary artery bypass grafting

CV, cardiovascular

HF, heart failure

HFmrEF, heart failure with mid-range ejection fraction

HFpEF, heart failure with preserved ejection fraction

HFrEF, heart failure with reduced ejection fraction

LVEF, left ventricular ejection fraction

LMICs, low- or middle-income countries

MRA, mineralocorticoid receptor antagonist

PCI, percutaneous coronary intervention

Introduction

Despite advances in care, patients recently hospitalized for acute heart failure (AHF) still have a high mortality[1–4]. Evidence-based practice guidelines[5,6] recommend that patients with HF and reduced left ventricular ejection fraction (HFrEF) are treated with angiotensin-converting enzyme inhibitors (ACEi)[7,8] or angiotensin receptor blockers (ARBs)[9,10], β-blockers[11] and mineralocorticoid receptor antagonists (MRAs)[12–14]. Early initiation of these guideline-recommended medications following hospitalization for HF improves outcomes[15]. Unfortunately, many patients with HFrEF do not receive these lifesaving medications at all or only on less than guideline-recommended target doses (GRTD)[16–19].

We previously showed that post-discharge mortality was substantially worse in patients with HFrEF from low- or middle-income countries (LMICs) in the prospective REPORT-HF registry[20]. It is unclear whether this finding reflects differences in patient characteristics, quality of discharge care, or access to guideline-recommended medical therapy. Reports from Western Europe and the United States suggest less than 20% of patients with HFrEF were on guideline-recommended doses of ACEi/ARBs, β-blockers, and MRAs[16–18]. Furthermore, in LMICs in Asia, substantial underutilization of guideline-recommended medical therapy exists[18].

This analysis aimed to assess (1) the prescription patterns of guideline-recommended therapy at discharge and 6-month follow-up for patients with AHF; (2) factors associated with use in countries at different economic levels; and (3) the association of medication prescribing with 12-month mortality.

Methods

Study Design, Setting, Participants, and Study Procedures.

Design, methods, and 1-year outcomes of the REPORT-HF study have been published[4,21–23]. In summary, REPORT-HF was a prospective, observational, global cohort study with patients prospectively enrolled from 6 continents, 44 countries, and 358 sites. This study was conducted per the Declaration of Helsinki, and the protocol received Institutional Review Board and/or ethics committee approval at each participating center. Participants were hospitalized with a primary diagnosis of AHF, according to the treating physician. Written informed consent was obtained from all patients or a legal representative. Potential participants unwilling or unable to provide informed consent were excluded. Patients were also excluded when they concurrently participated in a clinical trial with any investigational treatment.

Data were collected on patient's demographics, medical history, vital signs, laboratory values, acute therapies, procedures, hospital course, length of stay, and mortality in a central electronic database using the same case report form at all sites. Data was reviewed by central data-management and queries resolved by local study monitors. HFrEF was defined as an LVEF <40%, in keeping with current guidelines[24]. CAD was defined as having a history of coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), acute coronary syndrome or myocardial infarction. Anemia was defined as having a history of anemia or having a hemoglobin at <12 g/dL in women and <13 g/dL in men. Valvular heart disease was defined as a history of valvular heart disease or having valvular heart disease as an etiology. There were programmed database edit checks and manual data-review with queries when no information was filled in or in cases of data conflicts.

Collection of data on medication

Data on medication at discharge and 6-months after discharge were captured. Medication and doses at discharge were captured by investigators from medical records at or around the time of discharge during the index hospitalization. Medication information during follow-up was acquired from the treating physician or patients during a regular follow-up visit. If patients had no scheduled follow-up visit with the hospital where the initial index hospitalization took place, prescribing data were obtained by telephone from the primary care provider and/or patient at 6-months. There were programmed database edit checks and manual data-review with queries if no medications were recorded or doses/units were out of range for any of the cardiovascular (CV) drugs. Additional data-quality checks were performed using the records provided at the analysis stage. The fractionated target dose of ACEi/ARB/ angiotensin receptor neprilysin inhibitor (ARNi), β-blockers and MRAs was calculated based on GRTD according to the European Society of Cardiology and American Heart Association guidelines[5,6] (*supplementary table 1*). When no medications were recorded at discharge or follow-up visits, it was assumed that these data were missing, because it is unlikely that a patient would not be taking any medication. When one or more medications were recorded (e.g., - a diuretic or hypoglycemic agent) but this did not include one or more guideline-recommended treatments for HF (ACEi/ARB/ARNi, β-blockers, MRAs), it was assumed that these agents had not been prescribed. In total, paired medication data was available in 6,827 patients with HFrEF at both discharge and follow-up; and analyses involving medication at follow-up are restricted to these patients.

Outcomes.

Follow-up information from study participants was collected via a telephone interview at 6 and 12 months unless a regular follow-up visit was planned at the investigator's site for routine care. Vital status was supplemented by national reporting databases where available[21]. Local investigators ascertained the cause of death and classified as CV, non-CV or unknown.

Statistical Analysis

We report differences in patient characteristics, medication use, and dose achieved according to country income levels. Countries were grouped by income level, based on the World Bank classification (*Supplementary table 2*) using gross national income (GNI) in 2017[25]. The 44 participating countries were grouped into seven geographic regions based on a modification of the World Health Organization classification[21] (S*upplementary table 2*). We showed medication use and doses according to regional income level and to geographic region ordered according to mean regional income level. In secondary analyses, we studied the effect of income inequality on medication use using the Gini coefficient, with zero (0%) representing absolute income equality and one (100%) indicating significant income inequality. For most countries, the Gini coefficients were obtained from the UN Development Programme, as described previously[4]. Data from the year closest to 2003 was used, allowing for a potential lag effect. For comparisons between groups, we used the one-way analysis of variance (ANOVA), Chi2-test or Mann-Whitney U-test for normally distributed continuous variables, categorical variables, and non-normally distributed continuous variables, respectively. Multivariable logistic regression analyses were performed to investigate variables associated with being on medication. Variables were selected based on clinical significance and expert opinion. Because the aim of REPORT-HF was to compare quality and usual care globally, measurement of NT-proBNP or BNP was not mandated and only reported

if measured by treating physicians. We classified natriuretic peptides in tertiles and included a missing category for patients who did not have NPs measured, to correcting for any measurement bias. To test whether country income level modified the association of sex with medication use, we performed a test of interaction between sex and country income level for medication use. To correct for treatment indication-bias in outcome analyses, the reported hazard ratios from Cox proportional hazards regression analyses were weighted by the inverse probability of receiving the given treatment (ACEi/ARB/ARNi, β-blockers or MRAs) at ≥50% of GRTD. The probability of receiving ≥50% of GRTD for a particular treatment in each patient was modelled using logistic regression with LASSO penalization based on a comprehensive list of 58 variables (Supplementary table 3). The optimal penalty parameter was determined by 10-fold cross-validation. The optimal penalty parameter was determined by 10-fold cross-validation. The confidence intervals were derived using robust sandwich estimators in the coxph package. The proportionality of hazards assumption was checked using statistical tests and graphical diagnostics on the basis of the Schoenfeld residuals. REPORT-HF was designed to assess clinical practice differences and availability of diagnostic tests and treatment. Therefore, the missingness of variables was considered non-random due to differences in local practice and availability. Thus, we did not impute data but transformed the variable to include missing values[22]. Continuous variables with missing values were transformed according to tertiles. A 4th category for "missing" was included to account for missing values. Similarly for categorical variables, a "missing" category was included. All analyses were performed in STATA, version 16.0 or R, version 3.4.2. A two-sided P-value of <0.05 was considered statistically significant.

Results.

Baseline characteristics.

During the study period between July 23, 2014, and March 24, 2017, 18,553 patients were enrolled including 8,904 with HFrEF of whom 8,669 survived to discharge. The population's median age was 64 (25^{th} and 75^{th} percentile 55-74) years, and 72% were men. Compared to patients from high-income countries, patients from low-income countries were younger (median age of 60 vs 67 years), more often of non-white ethnicity, and more often had new-onset HF than patients from high-income countries (*Table 1*). In total, 12% of patients from low-income countries were in NYHA class III/IV at discharge compared to 15% of patients in high-income countries. Patients from low-income countries had a lower known comorbidity burden, except for diabetes, which was more prevalent in low-income countries (47%) than high-income countries (37%).

Among patients from low-income countries, 24% did not have health insurance compared to only 3% in high-income countries. Furthermore, patients from low-income countries were less likely to see a doctor after discharge (47% vs. 69% in high-income countries); either a general practitioner (2% vs. 15% in high-income countries) or cardiologist (44% vs. 60% in high-income countries). This difference remained after correcting for health insurance differences ($P<0.001$ for all).

Medication at discharge and 6-month follow-up

At discharge, 3,189 patients (37%) were on all three medications, 29 patients (<1%) had missing data on medication. In low-income countries, 271 patients (19%) were on all three medications compared to 1,566 (41%) in high-income countries. Patients from low-income countries were less likely on any of three classes of medicines, including ACEi/ARB/ARNi (57% vs. 71% in high-income countries), β-blockers (52% vs. 84% in high-income countries), and MRA (45% vs. 59%

in high-income countries, *Figure 1A*). Furthermore, patients from low-income countries were less likely on ≥50% of GRTD for ACEi/ARB/ARNi (22% vs. 28% in high-income countries) and β-blockers (7% vs. 32% in high-income countries) but were more often on GRTD for MRA (14% vs. 9% in high-income countries, *Figure 1A*).

At 6-months, data were missing on medication for 625 (8%) of patients. Among the 6,827 patients with medication data available at both discharge and 6 months, 5% of patients from low-income countries compared to 10% of patients in high-income countries for ACEI/ARB/ARNi were uptitrated (*Figure 1B*). For β-blockers 6% of patients from low-income countries were uptitrated to GRTD compared to 12% of high-income countries. For MRAs, patients from low-income countries were equally likely to be uptitrated at 6-months (4%) than patients from high-income countries (4%).

Patients without health insurance were less likely on ACEi/ARB/ARNi (57% vs. 68%), β-blockers (57% vs. 78%) and MRAs (46% vs. 62%) compared to patients with public insurance (*Figure 1C*). They were less likely on GRTD for ACEi/ARB/ARNi (28%), β-blockers (11%), and MRAs (10%) compared to patients with public insurance (28%, 27%, and 15% for ACEi/ARB/ARNi%, β-blockers, and MRAs respectively, *Figure 1C*). Only 51% of patients from low-income countries without insurance were on ACEi/ARB/ARNi, 41% on β-blockers, and 37% on MRAs compared to 70%, 83%, and 59% of patients with public insurance in high-income countries for ACEi/ARB/ARNi, β-blockers and MRA respectively (*Supplementary figure 1).* Patients without insurance were less likely uptitrated to GRTD compared to patients with private or public insurance for any medication class (*Figure 1D*). When stratified according to regions ordered by mean country income level, medication use was lowest in southeast Asia for all three

classes and highest in Western Europe (*Supplementary figure 2*). There was considerable heterogeneity among countries within regions (*supplementary figure 3*) as well.

Factors associated with medication use

In multivariable analyses, women, older patients, patients with new-onset HF, patients with CKD, patients from low-income countries, and patients without insurance were less likely to be on ACEI/ARBs/ARNis, β-blockers and MRAs at discharge (*Figure 3A-C*) and 6-months (*Supplementary figure 4A-C*). At 6-month follow-up, 22% of women from low-income countries were not on any medication than 5% of men from high-income countries. In sensitivity analyses we replaced history of hypertension by systolic blood pressure. Results remained similar (*Supplementary figure 5).* We did not observe a significant interaction P-value between sex and country income level for any of the three medication groups. *Supplementary figure 6* shows secondary analyses including country income disparity (Gini coefficient). Patients from countries with higher income disparity were less likely to be prescribed ACEi/ARB/ARNi or β-blockers at discharge than patients from countries with low-income disparity. Income disparity did not have a consistent effect on the likelihood of receiving an MRA at discharge.

Association with survival

In total, 1,819 (22%) patients died within one year. Mortality rates at 1-year were higher among patients from low-income countries (25%) compared to high-income countries (19%, P<0.001). Patients not on any of the three guideline-recommended classes of medicines at discharge were more likely to die (31%) compared to patients on at least one medication (21%). After adjusting for indication bias, patients up-titrated to ≥50% of GRTD had lower mortality compared to other patients, even after adjusting for treatment indication-bias for ACEi/ARB/ARNis (hazard ratio

[HR]: 0.70; 95% confidence interval (CI) 0.64-0.76), β-blockers (HR: 0.68; 95%CI 0.63-0.75) and MRAs (HR: 0.88; 95%CI 0.81-0.96) (*supplementary table 4, supplementary figure 7*). Results at 6 months were similar for all classes, except for MRAs (*supplementary table 4*).

Discussion

Pharmacological treatment is the cornerstone in the management of HFrEF. Yet, effective guideline-recommended medications for HF are underused and underdosed globally [16,17,26]. Our analysis adds to this evidence by demonstrating three principal findings and highlights the need for enhanced implementation of evidence-based medication for patients with HF globally. First, there is more undertreatment of patients with HF in low-income countries than patients from high-income countries. Second, underuse and sub-target dosing are particularly common in women and patients without health insurance. Six months after discharge—an appropriate time frame to ensure stability and initiate and up-titrate ACEi/ARB/ARNis, β-blockers and MRAs to target- or the maximally tolerated dose—almost 9% of patients did not receive any recommended pharmacological agents despite the clear guideline recommendations. Third, underuse of medications and target dosages were associated with increased mortality. In REPORT-HF, one-fifth of women in low-income countries were not on any of the three essential disease-modifying medicines at 6 months after discharge, compared to less than one in twenty men from high-income countries. The findings highlight broad implications beyond health policy since health and social exposures are closely intertwined. To address disparities in prescribing, we suggest that broader changes in policy (i.e., social, economic and health policy) are necessary to close the gap.

Our findings add to prior regional studies by evaluating medication prescribing and up-titration across multiple regions simultaneously. Despite clear survival benefits[27], various studies

have shown suboptimal prescribing of guideline-recommended medication in patients with HF[16–18,28–30], however these studies were from single countries[16,30], regions[17,18], or exclusively from higher income countries. Our results extend these earlier findings in several important ways, by including (1) global contemporaneous representation of a large number of countries, including many categorized as low-income, (2) data on medication and titration at different time points, and (3) in-depth patient-data on planned follow-up visits and insurance coverage. In Western Europe, only about half of patients with HFrEF were on ≥50% of GRTD for ACEi/ARBs and 40% for β-blockers[17]. In the United States, 23% of patients were on ≥50% of GRTD for ACEi/ARBs and 36% for β-blockers in the CHAMP-HF registry[16,26]. In the recent QUALIFY registry, prescription rates of ACEi/ARB (87%) and β-blockers (87%) were higher than prior research. However, this study predominantly included patients from high-income countries. Furthermore, patients with a HF hospitalization in the previous six months were excluded[31]. Trends of prescription rates in REPORT-HF parallel findings from these previous studies: only 36% and 44% of patients from Western Europe were on GRTD for ACEi/ARBs and β-blockers respectively; in North America, 28% of patients were on ≥50% of GRTD at 6 months for ACEi/ARBs and 39% for β-blockers. Notably, use and doses of MRA were higher in many lower income regions, possibly driven by the low cost of spironolactone and policies encouraging its use. For example, the use of MRAs in China was particularly high in our study, confirming earlier results[18]. This might be attributed to a nationwide quality assessment evaluation program evaluating spironolactone use during hospitalization[32] or treatment of co-existing hypertension[33]. Furthermore, seeing a general practitioner or cardiologist after discharge was an independent predictor of being on medication at 6-months after discharge, highlighting the vital role that healthcare practitioners outside of cardiology can play in initiating HF medication. Beyond country income level, there was

considerable geographic heterogeneity. For example, medication use and dosages of most pharmacotherapeutic classes was lower in Southeast Asian and Western Pacific countries when compared with countries in Western Europe or North America. The ESC Heart Failure Association Atlas recently highlighted the important regional heterogeneity of medication use and uptake, even within Europe. Higher income regions in Europe had more dedicated HF centres and more complete reimbursement of GDMT, particularly ARNi, than middle income regions. These previous data suggested that reimbursement might be an important factor in determining utilization of GDMT[34]. Our findings extend on this by further highlighting the importance of reimbursement: GDMT utilization was lower in patients without health insurance and in lower income regions, where patients often have higher out-of-pocket costs. Country income disparity showed an independent association with being prescribed ACEi/ARB/ARNi or β-blockers at discharge. This suggests an important part of the variance of medication use and doses may be explained by other factors such as local/regional practices and standards and income inequality, rather than country income level alone. Future clinical trials in (A)HF might benefit from examining the consistency of results by classifying countries not only by geography but also by income and income disparity.

Previous data from Asia, suggest stark regional differences in guideline-recommended medicines. China had the lowest prescription rate of ACEi/ARBs (60%) but the highest prescription rate of MRA (78%) in the ASIAN-HF registry[18], which is similar to REPORT-HF (57% and 86% ACEi/ARBs and MRAs respectively). Besides, patients from lower-income countries in ASIAN-HF were more often on sub-target, similar to REPORT-HF. Taken together, data from REPORT-HF are consistent with previous country-based or regional reports. Our results extend upon these earlier findings in several important ways, by including (1) global representation

of low-income countries, (2) data on medication and titration at different time points, and (3) in-depth patient-data on planned follow-up visits and insurance coverage.

Patients from low-income countries, those without health insurance, and women were least likely to be on guideline-recommended medical therapies and below GRTD. To the authors' knowledge, this is the first study showing underuse and sub-target dosing of lifesaving HF medications in low-income countries in a global registry with broad representation and highlights the need for targeted public health interventions to increase the quality of care and prescription of guideline-recommended therapy in HF. Individual patient factors like renal function, age, blood pressure, and heart rate might determine the prescription and dosing of pharmacotherapy for HFrEF. These factors, however, likely do not explain the observed regional differences – patients in lower-income countries were almost a decade younger in REPORT-HF and had a lower prevalence of relevant risk factors, including renal dysfunction and COPD[4]. Another explanation might be a patient's perception and familiarity with HF therapy. A recent survey in the US highlighted that a significant proportion of patients with HF were not familiar with guideline-directed medical therapy and questioned their effectiveness[35]. Our results show that economic factors might play a role[36]. In the Prospective Urban Rural Epidemiological (PURE) study, secondary preventative medicines for cardiovascular disease were underused globally, particularly in low-income countries[37–40]. Importantly, β-blockers and ACEis were considered unaffordable even for participants in the highest household wealth groups in low-income countries[39]. While we did not investigate ARNi or SGLT-2 inhibitors separately, uptake will likely be even lower for these more expensive but lifesaving treatment options[41]. Together, our data suggest the underuse of ACEi/ARBs, MRAs, and β-blockers in patients without health insurance, indicating that insurance coverage and medication costs might be a possible governing factor determining access.

Our results suggest a survival benefit for achieving ≥50% of GRTD for ACEi/ARB/ARNis and β-blockers, after accounting for treatment indication-bias, and regardless of region or economic status. We tried to correct for confounding factors as much as possible. However, REPORT-HF was not a randomized trial and, therefore, our results should be interpreted with caution. For example, we did not observe a survival benefit for MRAs. Patients with a worse NYHA class and longer length of stay were more likely to be prescribed an MRA. Therefore, the absence of a clear association with survival of MRAs might be driven by (residual) confounding, despite the use of inverse probability weighting. The benefits of MRAs for patients with HFrEF are well established in randomized trials[14,23]. Thus, the analyses of REPORT-HF should not be used to determine treatment decisions for individual patients. Observational data can be used to assess outcomes associated with a treatment, but randomized trials are required to determine the response to treatment; these are very different concepts[42]. However, our results highlight the window of opportunity to initiate HF medication before discharge, the importance of adequate discharge planning and the need for follow-up by someone with the appropriate expertise.

Strengths and limitations of study

Strengths of this study include the prospective design and the global representation of patients with different ethnicities from countries at different economic levels. The study's limitations include non-random sampling of centers and countries, done for practical reasons and lack of establishment on causality or drug efficacy. Therefore, present results likely represent a 'best-case scenario – centers serving more rural populations are probably not well represented. While we have performed inverse probability weighting to account for confounding in outcome analyses, residual confounding can unfortunately not be measured. Furthermore, no reasons for sub-target dosing, contraindications or adverse events were captured in the database. Likewise, it is unclear

412 if patients not receiving target doses were on maximally tolerated doses or not, and we did not
413 assess adherence. Besides, it is possible that some patients not receiving medications or receiving
414 low doses have previously tried the medication but did not tolerate it. However, given the more
415 favorable risk profile of patients from low-income countries, including a lower prevalence of
416 hypotension and renal dysfunctions, differences in contraindications likely do not explain the
417 differences in prescription patterns between income regions but are possibly the consequence of
418 economic limitations or clinical inertia. Given the need for patients to consent to participate in
419 REPORT-HF, selection bias might have taken place. Furthermore, fractions of GRTD might be
420 confounded by individual patient characteristics (weight of the patient, frailty, blood pressure,
421 renal function) and decisions of individual healthcare practitioners, which might have introduced
422 bias. If updated prescribing information was not available from the participants medical records,
423 it was obtained by telephone from the primary care provider or patient. Finally, patients in
424 REPORT-HF were hospitalized, and a relatively higher risk population. However, given the lack
425 of data on prescription rates and dosages of HF medications, especially in LMICs, the present
426 study is the best available evidence to date for these patients.

427 ***Conclusions.***

428 REPORT-HF highlights the global sub-optimal implementation of treatment with
429 ACEi/ARBs/ARNis, β-blockers, and MRAs for patients with HFrEF. Underuse and sub-target
430 dosing are especially common in low-income countries. Prescription of all three classes of
431 guideline-recommended medicines was low among women, low-income countries, and patients
432 without health insurance. These results add to existing literature showing economic disparity in
433 quality and access to care. Furthermore, our results emphasize the need for better optimization of
434 HF therapy through increasing access to good-quality care, targeting social and health care policy,

improving physician education, better discharge planning, and post-discharge involvement and education of other (primary) care providers.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2006;**355**:251–259.

2. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. *Circulation* 2002;**106**:3068–3072.

3. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanas F, Prabhakaran D, Badr A, Elmaghawry M, Damasceno A, Tibazarwa K, Belley-Cote E, Balasubramanian K, Islam S, Yacoub MH, Huffman MD, Harkness K, Grinvalds A, McKelvie R, Bangdiwala SI, Yusuf S, Campos R, 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**:e665–e672.

4. Tromp J, Bamadhaj S, Cleland JGF, Angermann CE, Dahlstrom U, Ouwerkerk W, Tay WT, Dickstein K, Ertl G, Hassanein M, Perrone S V., Ghadanfar M, Schweizer A, Obergfell A, Lam CSP, Filippatos G, Collins SP. Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and national level of income and income disparity (REPORT-HF): a cohort study. *Lancet Glob Heal* 2020;**8**:e411–e422.

5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der, Filippatos G, McMurray JJV, Aboyans V, Achenbach S, Agewall S, Al-Attar N, Atherton JJ, Bauersachs J, Camm AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.

6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld JA, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on

Clinical Practice Guidelines and the Heart Failure Society of Amer. *Circulation* 2017;**136**:e137–e161.

7. Investigators TS. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.

8. Swedberg K, Idanpaan-Heikkila U, Remes J. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435.

9. McMurray JJV, Östergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-added trial. *Lancet* 2003;**362**:767–771.

10. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Östergren J, Pfeffer MA, Swedberg K. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-alternative trial. *Lancet* 2003;**362**:772–776.

11. Dargie HJ, Lechat P. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999;**353**:9–13.

12. Zannad F, McMurray JJV, Krum H, Veldhuisen DJ van, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. *N Engl J Med* 2011;**364**:11–21.

13. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. *N Engl J Med* 2003;**348**:1309–1321.

14. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *N Engl J Med* 1999;**341**:709–717.

15. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med* 2019;**380**:539–548.

16. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. *J Am Coll Cardiol* 2018;**72**:351–366.

17. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, Harst P Van Der, Hillege HL, Lang CC, Maaten JM Ter, Ng LL, Ponikowski P, Samani NJ, Veldhuisen DJ Van, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: A prospective European study. *Eur Heart J* 2017;**38**:1883–1890.

18. Teng THK, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, Wander GS, Yap JJ, MacDonald MR, Xu CF, Chia YM, Shimizu W, Richards AM, Voors A, Lam CS.

513 Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the
514 ASIAN-HF registry: a cohort study. *Lancet Glob Heal* 2018;**6**:e1008–e1018.

515 19. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS. Physicians'
516 guideline adherence is associated with better prognosis in outpatients with heart failure
517 with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail*
518 2017;**19**:1414–1423.

519 20. MacDonald MR, Tay WT, Teng THK, Anand I, Ling LH, Yap J, Tromp J, Wander GS,
520 Naik A, Ngarmukos T, Siswanto BB, Hung CL, Richards AM, Lam CSP. Regional
521 Variation of Mortality in Heart Failure With Reduced and Preserved Ejection Fraction
522 Across Asia: Outcomes in the ASIAN-HF Registry. *J Am Heart Assoc* 2020;**9**:e012199.

523 21. Filippatos G, Khan SS, Ambrosy AP, Cleland JGF, Collins SP, Lam CSP, Angermann
524 CE, Ertl G, Dahlström U, Hu D, Dickstein K, Perrone S V., Ghadanfar M, Bermann G,
525 Noe A, Schweizer A, Maier T, Gheorghiade M. International REgistry to assess medical
526 Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF):
527 Rationale for and design of a global registry. *Eur J Heart Fail* 2015;**17**:527–533.

528 22. Filippatos G, Angermann CE, Cleland JGF, Lam CSP, Dahlström U, Dickstein K, Ertl G,
529 Hassanein M, Hart KW, Lindsell CJ, Perrone S V., Guerin T, Ghadanfar M, Schweizer A,
530 Obergfell A, Collins SP. Global Differences in Characteristics, Precipitants, and Initial
531 Management of Patients Presenting with Acute Heart Failure. *JAMA Cardiol* 2020;**5**:401–
532 410.

533 23. Tromp J, Ouwerkerk W, Cleland JGF, Angermann CE, Dahlstrom U, Tiew-Hwa Teng K,
534 Bamadhaj S, Ertl G, Hassanein M, Perrone S V., Ghadanfar M, Schweizer A, Obergfell A,
535 Filippatos G, Collins SP, Lam CSP, Dickstein K. Global Differences in Burden and
536 Treatment of Ischemic Heart Disease in Acute Heart Failure: REPORT-HF. *JACC Hear*
537 *Fail* JACC Heart Fail; 2021;**9**:349–359.

538 24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V,
539 González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos
540 P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH,
541 Meer P Van Der. 2016 ESC Guidelines for the diagnosis and treatment of acute and
542 chronic heart failure. *Eur Heart J* 2016;**37**:2129-2200m.

543 25. World Bank. World Bank Country and Lending Groups – World Bank Data Help Desk.
544 World Bank. 2017. p. 1–8.
545 https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 (23 September 2020)

546 26. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, Duffy
547 CI, Hill CL, McCague K, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez
548 AF, Butler J. Titration of Medical Therapy for Heart Failure With Reduced Ejection
549 Fraction. *J Am Coll Cardiol* 2019;**73**:2365–2383.

550 27. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA.
551 Potential impact of optimal implementation of evidence-based heart failure therapies on
552 mortality. *Am Heart J* 2011;**161**.

553 28. Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Pannaux M, Swedberg K. Incremental

benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fail* 2018;**20**:1315–1322.

29. Motiejunaite J, Akiyama E, Cohen-Solal A, Maggioni A Pietro, Mueller C, Choi DJ, Kavoliuniene A, Celutkiene J, Parenica J, Lassus J, Kajimoto K, Sato N, Miró Ò, Peacock WF, Matsue Y, Voors AA, Lam CSP, Ezekowitz JA, Ahmed A, Fonarow GC, Gayat E, Regitz-Zagrosek V, Mebazaa A. The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions. *Eur Heart J* 2020;**41**:1357–1364.

30. Srivastava PK, DeVore AD, Hellkamp AS, Thomas L, Albert NM, Butler J, Patterson JH, Spertus JA, Williams FB, Duffy CI, Hernandez AF, Fonarow GC. Heart Failure Hospitalization and Guideline-Directed Prescribing Patterns Among Heart Failure With Reduced Ejection Fraction Patients. *JACC Hear Fail* 2021;**9**:28–38.

31. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, Tavazzi L. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: Data from the QUALIFY global survey. *Eur J Heart Fail* 2016;**18**:514–522.

32. Guan W, Murugiah K, Downing N, Li J, Wang Q, Ross JS, Desai NR, Masoudi FA, Spertus JA, Li X, Krumholz HM, Jiang L. National quality assessment evaluating spironolactone use during hospitalization for acute myocardial infarction (AMI) in China: China Patient-centered Evaluation Assessment of Cardiac Events (PEACE)-Retrospective AMI Study, 2001, 2006, and 2011. *J Am Heart Assoc* 2015;**4**:e001718.

33. Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007;**49**:839–845.

34. Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R, Kazakiewicz D, Coats AJS, Berger R, Jahangirov T, Kurlianskaya A, Troisfontaines P, Droogne W, Hudic LD, Tokmakova M, Glavaš D, Barberis V, Spinar J, Wolsk E, Uuetoa T, Tolppanen H, Kipiani Z, Störk S, et al. The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. *Eur J Heart Fail* 2021;**23**:906–914.

35. Samsky MD, Lin L, Greene SJ, Lippmann SJ, Peterson PN, Heidenreich PA, Laskey WK, Yancy CW, Greiner MA, Hardy NC, Kavati A, Park S, Mentz RJ, Fonarow GC, O'Brien EC. Patient Perceptions and Familiarity with Medical Therapy for Heart Failure. *JAMA Cardiol* 2020;**5**:292–299.

36. Fonarow GC, Navar AM, Yancy CW. Impediments to Implementing Guideline-Directed Medical Therapies. JAMA Cardiol. American Medical Association; 2019. p. 830–831.

37. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, Kruger A, Kutty R, Lanas F, Liu L, Wei L, Lopez-Jaramillo P, Oguz A, Rahman O, Swidan H, Yusoff K, Zatonski W, Rosengren A, Teo KK. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective

epidemiological survey. *Lancet* 2011;**378**:1231–1243.

38. Murphy A, Palafox B, O'Donnell O, Stuckler D, Perel P, AlHabib KF, Avezum A, Bai X, Chifamba J, Chow CK, Corsi DJ, Dagenais GR, Dans AL, Diaz R, Erbakan AN, Ismail N, Iqbal R, Kelishadi R, Khatib R, Lanas F, Lear SA, Li W, Liu J, Lopez-Jaramillo P, Mohan V, Monsef N, Mony PK, Puoane T, Rangarajan S, Rosengren A, et al. Inequalities in the use of secondary prevention of cardiovascular disease by socioeconomic status: evidence from the PURE observational study. *Lancet Glob Heal* 2018;**6**:e292–e301.

39. Khatib R, McKee M, Shannon H, Chow C, Rangarajan S, Teo K, Wei L, Mony P, Mohan V, Gupta R, Kumar R, Vijayakumar K, Lear SA, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, Yusoff K, Ismail N, Kazmi K, Rahman O, Rosengren A, Monsef N, Kelishadi R, Kruger A, Puoane T, Szuba A, Chifamba J, Temizhan A, Dagenais G, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: An analysis of the PURE study data. *Lancet* 2016;**387**:61–69.

40. Langhorne P, O'Donnell MJ, Chin SL, Zhang H, Xavier D, Avezum A, Mathur N, Turner M, MacLeod MJ, Lopez-Jaramillo P, Damasceno A, Hankey GJ, Dans AL, Elsayed A, Mondo C, Wasay M, Czlonkowska A, Weimar C, Yusufali AH, Hussain F Al, Lisheng L, Diener HC, Ryglewicz D, Pogosova N, Iqbal R, Diaz R, Yusoff K, Oguz A, Wang X, Penaherrera E, et al. Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study. *Lancet* 2018;**391**:2019–2027.

41. Sandhu AT, Heidenreich PA. The Affordability of Guideline-Directed Medical Therapy: Cost Sharing is a Critical Barrier to Therapy Adoption. *Circulation* 2021;**143**:1073–1075.

42. Cleland JGF, Ghio S. The determinants of clinical outcome and clinical response to CRT are not the same. *Heart Fail Rev* 2012;**17**:755–766.

Figure Legends

Figure 1: Stacked bar chart depicting the proportion of patients at discharge on guideline recommended therapy and ≥50 of target dose at discharge stratified to country income level (A) uptitration of patients between discharge and 6-months follow-up stratified to country income level (B) proportion of patients at discharge on guideline recommended therapy and ≥50 of target dose at discharge stratified to insurance status (C) uptitration of patients between discharge and 6-months follow-up stratified to insurance status (D).

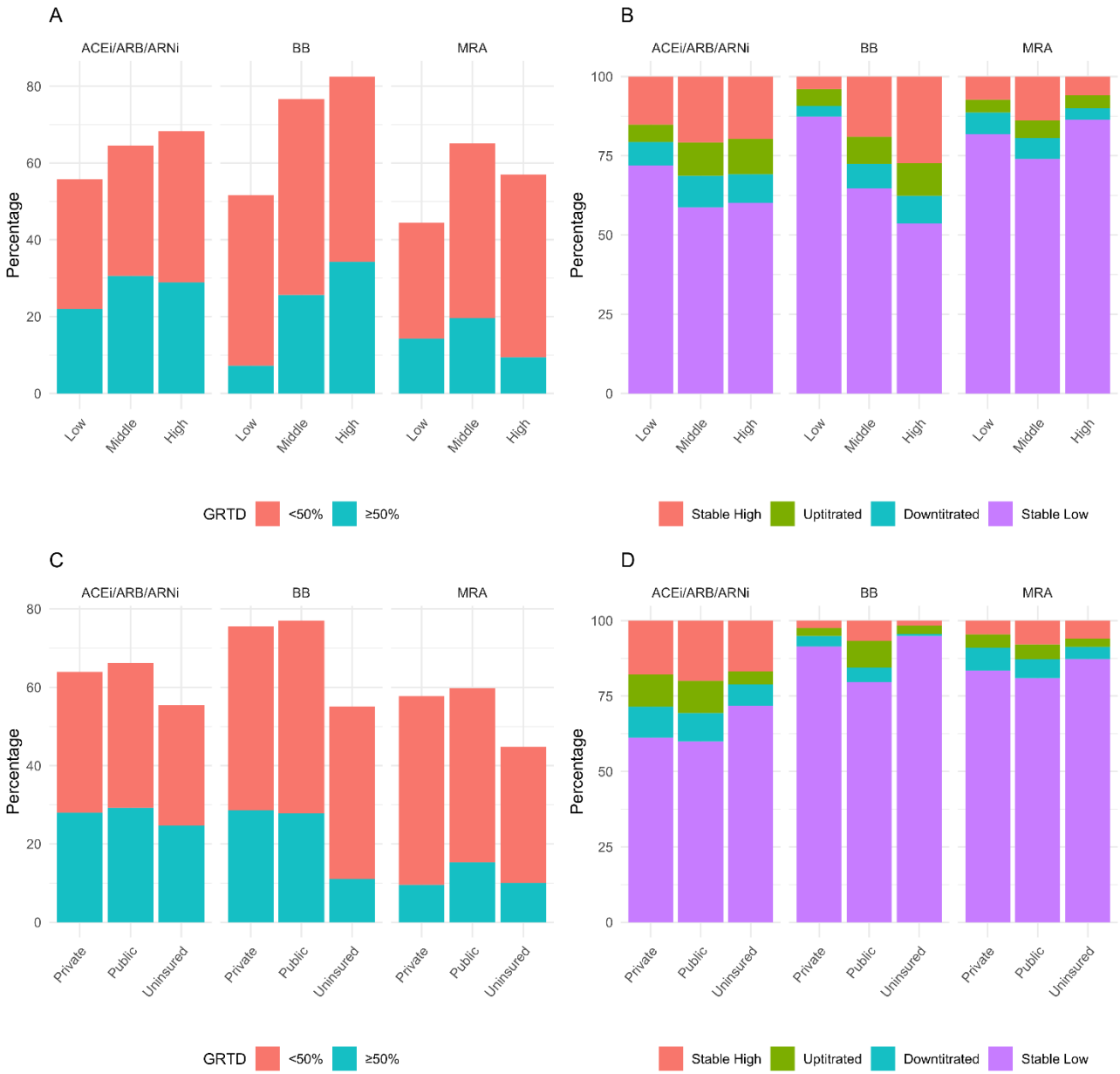
A
ACEi/ARB/ARNi
BB
MRA
Percentage
0
20
40
60
80
Low
Middle
High
GRTD
<50%
≥50%
B
100
75
50
25
Stable High
Uptitrated
Downtitrated
Stable Low
C
Private
Public
Uninsured
D

Figure 2: World maps for average dosages of guideline recommended medical therapy at discharge among patients on medication for ACEi/ARB/ARNi, β-blockers and MRA.

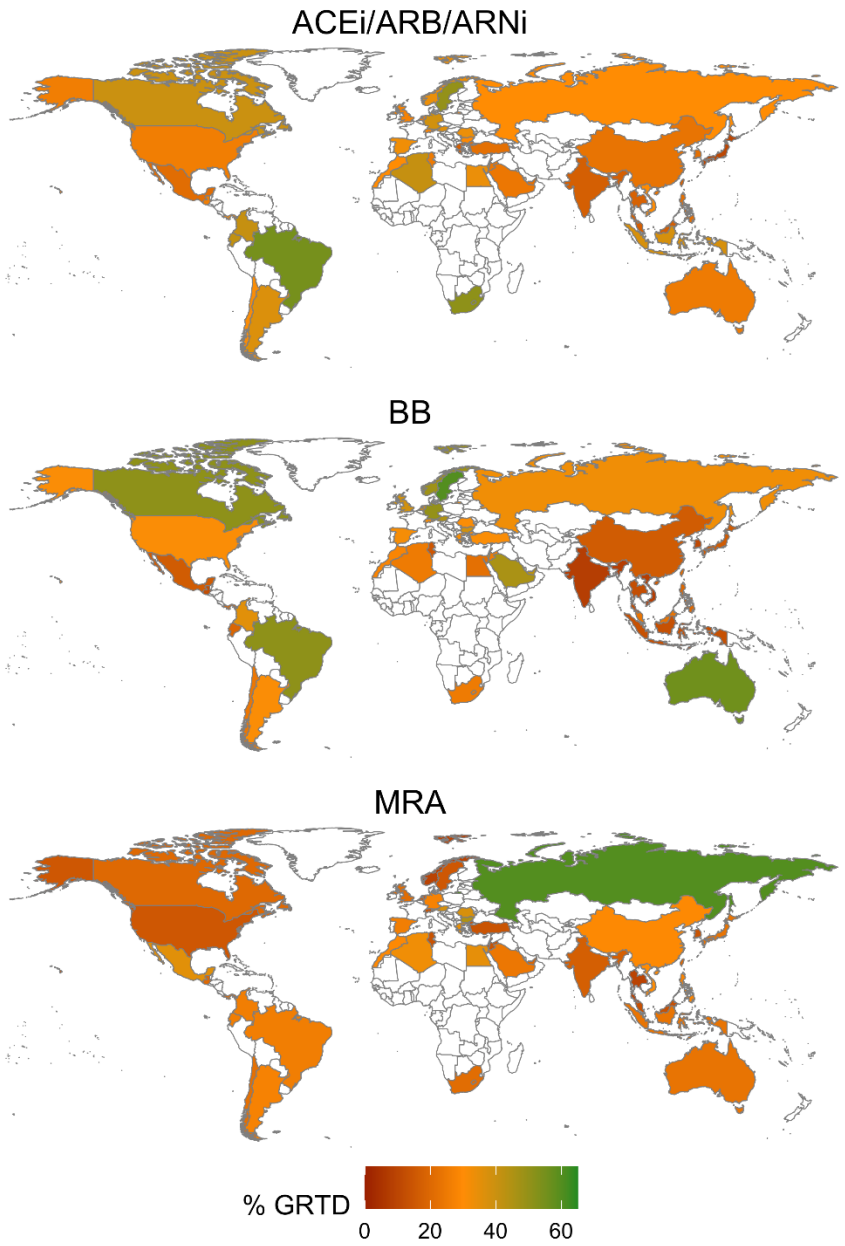
ACEi/ARB/ARNi
BB
MRA
% GRTD
0
20
40
60

Figure 3: Panel figure showing forest plots for multivariable logistic regression with factors associated with being on (A) ACEi/ARBs, (B) β-blockers and (C) MRAs at discharge.