Global Differences in Burden and Treatment of Ischemic Heart Disease in Acute Heart Failure: REPORT-HF

Short title: Global differences in ischemic heart disease in acute heart failure

Jasper Tromp*[1], MD PhD; Wouter Ouwerkerk[2,3] PhD; John G. F. Cleland[4], MD; Christiane E. Angermann[5], MD; Ulf Dahlstrom[6], MD; Katherine Tiew-Hwa Teng[2], PhD; Sahiddah Bamadhaj[2], BSc; Georg Ertl[5], MD; Mahmoud Hassanein[7], MD; Sergio V. Perrone[8], MD; Mathieu Ghadanfar[9] MD; Anja Schweizer[10], PhD; Achim Obergfell[10], MD; Gerasimos Filippatos[11], MD; Sean P Collins[12], MD; Carolyn SP Lam[1], MBBS PhD; Kenneth Dickstein*[13], MD PhD

1. National Heart Centre Singapore & Duke-National University of Singapore, Singapore; University Medical Centre Groningen, the Netherlands
2. National Heart Centre Singapore, Singapore
3. Dept of Dermatology, Amsterdam UMC, University of Amsterdam, Amsterdam Infection & Immunity Institute, Amsterdam, The Netherlands
4. Robertson Centre for Biostatistics and Clinical Trials, Institute of Health & Well-Being, University of Glasgow and National Heart & Lung Institute, Imperial College, London.
5. University and University Hospital Würzburg, Comprehensive Heart Failure Center, Würzburg, Germany
6. Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linkoping University, Linkoping, Sweden
7. Alexandria University, Faculty of Medicine, Cardiology Department Alexandria, Egypt
8. El Cruce Hospital by Florencio Varela, Lezica Cardiovascular Institute, Sanctuary of the Trinidad Miter, Buenos Aires, Argentina
9. M-Ghadanfar Consulting (Life Sciences), Basel, Switzerland
10. Novartis Pharma AG, Basel, Switzerland
11. University of Cyprus, School of Medicine & National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece
12. Vanderbilt University Medical Center, Department of Emergency Medicine, Nashville, TN, USA
13. University of Bergen, Stavanger University Hospital, Norway

***Corresponding authors:**

Jasper Tromp. MD PhD.
National Heart Centre Singapore, Singapore. University Medical Centre Groningen, the Netherlands.
E-mail: j.tromp01@umcg.nl

Kenneth Dickstein, MD PhD
Department of Cardiology, Stavanger University Hospital, Stavanger, Norway; Institute of Internal Medicine, University of Bergen, Bergen, Norway.
Email: kenneth.dickstein@med.uib.no.

Conflicts of interest:

REPORT-HF: was funded by Novartis. C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen,

Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd and Corpus; and serves as co-founder & non-executive director of eKo.ai. J.T has received personal grants and speaker fees from Olink proteomics and Roche diagnostics. GF reports research grants from the European Union. Committee fees from Novartis related to REPORT-HF. Committee member in trials and/or registries sponsored by Servier, BI, Medtronic, Vifor. CEA reports grants, personal fees and other from Novartis. She further acknowledges non-financial support from the University Hospital Würzburg, non-financial support from the Comprehensive Heart Failure Center Würzburg and grant support from the German Ministry for Education and Research (BMBF). UD reports research support from Astra Zeneca, Pfizer, Boehringer Ingelheim, Vifor, Roche Diagnostics, Boston Scientific and speaker´s honoraria and consultancies from Astra Zeneca, Novartis and Amgen. MH received honoraria as a lecturer from Novartis, Aventis, Amgen, MSD, Astrazeneca and Merck. SPC reports research grants from NIH, AHRQ, AHA, PCORI and consulting fees from Novartis, Medtronic, Vixiar and Ortho Clinical. MG, AS and AO are employed by Novartis. JGFC reports grants and personal fees from Amgen, personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from Bristol Myers Squibb, grants, personal fees and non-financial support from Medtronic , personal fees from Myokardia, grants, personal fees and non-financial support from Novartis, grants and personal fees from Philips, grants and non-financial support from Pharmacosmos, grants and non-financial support from PharmaNord, personal fees from Sanofi, personal fees from Servier, grants and personal fees from Stealth Biopharmaceuticals, grants and personal fees from Torrent Pharmaceuticals, grants, personal fees and non-financial support from Vifor, personal fees from Abbott. The remaining authors have nothing to disclose.

Abstract

Background. Data on ischemic heart disease (IHD) in patients with acute heart failure (AHF) is primarily from Western Europe and North America. Little is known about global differences in treatment and prognosis of patients with IHD and AHF.
Methods. We prospectively enrolled 18,539 patients with AHF from 44 countries and 365 centers in the REPORT-HF registry. Patients with a history of coronary artery disease, an ischemic event causing admission for AHF or coronary revascularization were classified as IHD. Clinical characteristics, treatment and outcomes of patients with and without IHD were explored.
Results. Compared to 8,766 (47%) patients without IHD, 9,773 (53%) patients with IHD were older, more likely a left ventricular ejection fraction (LVEF) <40% (HFrEF), and more comorbidities. IHD was more common in lower compared to higher income countries (61% versus 48%). Patients with IHD from countries with low healthcare expenditure per capita, or without health insurance less likely underwent coronary revascularization, or used anticoagulants at discharge. IHD was independently associated with worse cardiovascular (CV) death (HR 1.21; 95%CI 1.09-1.35). The association between IHD and CV death was stronger in HFrEF compared to HF with preserved ejection fraction ($P_{interaction}$ <0.001).
Conclusion. In this large global contemporary cohort of patients with AHF, IHD was more common in low-income countries and conveyed worse 1-year mortality, especially in HFrEF. Patients in regions with the greatest burden of IHD, were less likely to receive coronary revascularization, and treatment for IHD.

Key words: heart failure, ischemic heart disease; evidence-based pharmacotherapy; outcomes

Introduction.

Ischemic heart disease (IHD) is a common cause of heart failure (HF)[1], and is associated with increased mortality[1–3]. Although the prevalence of risk factors for developing IHD is lower in low-income countries, the relative incidence and case-fatality rate of IHD is often higher. This is possibly caused by a combination of poor risk factor control, and worse health system quality[4,5].

In the INTER-CHF study, IHD was the primary etiology in 56% of patients with HF from Southeast Asia, and 45% of patients in China[6]. In the European Society of Cardiology (ESC) long-term registry[7], the prevalence of IHD was highest in Eastern Europe at 47%. Yet, both studies included a limited number of countries and no study investigated the global burden, and treatment of IHD in patients with HF in a prospective contemporary cohort.

The International Registry to Assess Medical Practice With Longitudinal Observation for Treatment of Heart Failure (REPORT-HF) is a global, prospective, and observational cohort study uniquely designed to assess differences in comorbidities and treatment of patients hospitalized for HF[8]. The primary aim of the present study, is to investigate global differences in prevalence, association with outcome, and treatment of IHD in patients with acute HF (AHF) in REPORT-HF.

Methods

Study Design and Setting.

Methods, design and 1-year outcomes of the REPORT-HF have been described before[9,10]. Briefly, REPORT-HF was an observational, prospective, global cohort study with patients

enrolled from 6 continents, 44 countries and 358 sites. Eligible patients were asked to give consent and enrolled consecutively or intermittent consecutively on pre-determined days of the week or weeks of the month. The original proposed sample size was 20,000 patients to analyze all comparisons of interest with an assumed attrition of 30%. The target sample was re-evaluated when ~50% of patients were recruited during a pre-specified interim analysis[8]. This resulted in a revised estimated attrition rate of ~25%. The following adjusted sample size was 18,700 for the total cohort. Enrollment took place between July 23, 2014 and March 24, 2017.

Participants and Study Procedures.

REPORT-HF was conducted in accordance with the declaration of Helsinki, and the protocol received Institutional Review Board and/or ethics committee approval at each participating center. All participants were hospitalized with a primary diagnosis of AHF, based on the judgement of the treating physician. Study investigators were encouraged to adhere to local standards and recommendations for the diagnosis and treatment of AHF. Written informed consent was required from all participants or a legal representative, if permitted. Patients unable or unwilling to provide consent, or patients participating in a clinical trial were excluded.

Data on patients' demographics, medical history, physical exam, vital signs, laboratory values, acute therapies, hospital course, procedures, length of stay and mortality were collected and captured in a central electronic database using the same case report form at all sites. A central data-management committee reviewed the data and raised queries where necessary. These were then resolved by local study monitors. HF with reduced ejection fraction (HFrEF) was defined as a left ventricular ejection fraction (LVEF) <40%, HF with mid-range ejection

fraction (HFmrEF) was defined as a LVEF 40-49% and HF with preserved ejection fraction (HFpEF) was defined as a LVEF of ≥50% in keeping with current guidelines[11]. LVEF was assessed in 82% of patients with a reported LVEF during the index hospitalization. When this was not available, the LVEF reported prior to the index hospitalization was used. IHD was defined as having a history of coronary artery disease, acute coronary syndrome (ACS) or myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary arterial bypass grafting (CABG) or ischemic etiology of HF. New-onset IHD was separately defined as having ACS/MI as a precipitant leading to hospitalization, having a PCI/CABG during the index hospitalization or experiencing a new-onset ACS/MI during the index hospitalization (supplementary table 1).

Collection of data on medication.

The exact time of first administration of all intravenous treatments for AHF was recorded; the time of arrival was similarly captured and the difference between the time of arrival and time of administration was defined at the door-to-treatment time. Medication data was captured at discharge and 6-months through follow up with the patient and/or primary care provided. Names of medical therapies, dosages and units were captured. Queries were raised by programmed database edit if no medications were recorded and manual review with queries were raised when doses/units were off. When no medications were recorded at follow-up visits, it was assumed that these data were missing, because it is unlikely that a patient would not be taking some 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, it was assumed that these agents had not been prescribed. We calculated maximum daily doses attained at discharge and 6 months follow up, among the proportion of patients on guideline

recommended β-blockers, ACEi/ARBs and mineralocorticoid receptor antagonists (MRAs) (Supplementary table 2).

Outcomes.

Standardized follow-up calls were performed at 6 months and one year. Unless a regular follow-up visit was planned at the investigator site for routine care, information from study participants was collected during telephone interviews. Vital status was supplemented by national recording databases were available. Causes of death were ascertained by the local investigators and captured as cardiovascular (CV) versus non-CV. Patients were considered lost to follow-up if no information was available on vital status, or any follow-up visit. Outcomes were not independently adjudicated.

Statistical Analysis

Differences in patient treatment are reported according to IHD status. Stratifications according to country spending on healthcare per capita purchasing power parity (PPP) provided by the World Bank, using 2017 as the reference year and country income level as reported previously were made[9]. In addition, the 44 participating countries were grouped. Comparisons between groups were tested using the Student's t-test, 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 factors associated with medication use. Variables were selected based on clinical significance and expert opinion. In addition, we corrected for the MAGGIC risk score[12], which includes LVEF, systolic

blood pressure, age, sex, body mass index (BMI), creatinine, New York Heart Association (NYHA) class, history of diabetes or COPD, time since diagnosis, use of ACEi/ARBs at discharge, use of beta-blockers at discharge. REPORT-HF was designed to assess differences in clinical practice, availability of diagnostic tests and treatment, therefore missingness of variables was considered to be not completely at random, but due to differences in local practice and availability as previously reported[9]. For the stepwise Cox model, 75 patients had missing data for any one of the variables, and were removed from further analyses. Due to missingness of systolic blood pressure, BMI, and creatinine, we used multiple imputation to calculate the MAGGIC risk score per patient. Imputation was performed using the Multivariate Imputation by Chained Equations (MICE) package in R, using default polytomous regression for multilevel factor variables, logistic regression for binary variables and predictive mean matching for continuous variables. Values were averaged over five imputation sets, and the risk score per patients was calculated based on the averaged values. For the LASSO regression analyses, variables were transformed to tertiles and included 'missing' as a separate factor level. Kaplan-Meier curves were used to graphically depict differences in 1-year mortality, while cumulative incidence curves were used for CV mortality. In all analyses for CV and non-CV mortality, deaths classified other than the outcome were considered as a competing risk. Multivariable analyses were performed using Cox regression analyses. The proportionality of hazards assumption was checked using statistical tests and graphical diagnostics on the basis of the Schoenfeld residuals. Patients without any follow-up data were excluded. Patients were censored at their date of death or last known follow-up date. To account for differences in facility level characteristics within countries, we allowed estimates of our logistic and Cox regression models to cluster around the center variable. We tested for interaction between history of IHD and HF subtype (HFrEF;

HFmrEF; HFpEF) for 1-year all-cause mortality. In sensitivity analyses, we restricted the test for interaction to patients with LVEF measured during the index hospitalization. To correct for treatment indication bias in outcome analyses of medication, we used inverse probability weighting (IPW). The probability of being on the drug was modelled using LASSO penalized regression analyses based on 73 variables (Supplementary Table 3). To find the optimal lambda in our LASSO regression, we performed ten cross validations to increase robustness[13]. Because we accounted for center effects in our logistic and survival models, we did not account for multiple testing. Due to the large sample size and small P-values in most comparisons made, we view the P-values considering the relative effect sizes and clinically important differences. A two-sided P-value of <0.05 was considered statistically significant.

Results.

Patient characteristics

Between July 23, 2014 and March 24, 2017, 18,539 patients were prospectively enrolled. In total, 9,773 (53%) patients had IHD. The prevalence of IHD ranged from 22% in Ecuador to 78% in Russia. The prevalence of IHD was higher in countries like China (56%) and India (60%), compared to the United States (48%). IHD was more common in Eastern Europe, Southeast Asia and the Western Pacific (Central illustration, Supplementary table 4). When stratified to country income level, the prevalence of IHD was higher (P <0.001) in lower-income countries (61%) than high-income countries (48%).

When stratified to medical history of IHD alone, or new onset IHD (supplementary table 4), 6627 (36%) patients had a medical history of IHD, and 3146 (17%) patients had new onset

IHD. In the eastern Mediterranean and Africa region, Southeast Asia and the Western Pacific, new onset IHD was more common (20%, 30% and 24% respectively) compared to other regions.

Patients with IHD were older, more often men, less often presented with new onset HF, had a higher NYHA class prior to admission, more likely a LVEF <50%, and more often had chest pain, and less often peripheral edema (Table 1). A medical history of hypertension, anemia, diabetes, chronic kidney disease and smoking was more common in patients with IHD compared to those without IHD.

Treatment characteristics

Door to any IV treatment time, door to vasodilator time and door to diuretic time were shorter in patients with IHD compared to those without (Table 2). After accounting for age, sex, NYHA class prior to admission, and regional income level, these associations were no longer significant (P for all >0.1). In total, 999 (10%) patients with IHD underwent a PCI during hospitalization and 116 (1.1%) a CABG (Table 2).

In total, 72(0.4%) patients had missing data on medication at discharge. In univariable analyses, patients from countries with lower healthcare expenditure more frequently underwent CABG/PCI during index hospitalization and were more often on P2Y12 inhibitors and aspirin at discharge, but less often on β-blockers (Figure 1A). In multivariable analyses compared to countries in the highest tertile of healthcare expenditure (Supplementary table 5), P2Y12 inhibitors at discharge were more often used in countries in the lowest healthcare expenditure tertile (odds ratio [OR] 1.78; 95%CI (1.40-2.26), while β-blockers at discharge (OR 0.30, 95%CI 0.23-0.39) or PCI/CABG during the index hospitalization (OR 0.57; 95%CI 0.47-0.70) were less often used. The association between country level health expenditure and aspirin and statin use at

discharge was no longer significant in multivariable analyses (P >0.05 for both, supplementary table 5).

When stratified to patient health insurance status (public/national; private; uninsured), patients without health insurance less often had β-blockers, but more often P2Y12 inhibitors at discharge (Figure 1B). PCI/CABG during hospitalization was less common in patients without health insurance compared to patients with health insurance. In multivariable analyses, patients without insurance were less likely on β-blockers at discharge (OR: 0.61; 95%CI 0.41-0.90), or underwent PCI/CABG during the index hospitalization (OR: 0.35, 95%CI 0.18-0.67, Supplementary table 6).

Outcome

At 1 year, 3461 (20%) patients died and 470 (2.7%) patients were lost to follow-up. Patients without IHD were more often lost to follow-up (260[3%]) compared to patients with IHD (210[2%]). Within 1 year, 1958 (21%) patients with IHD died compared to 1503 (18%) patients without IHD (Table 2, Figure 2). Patients with IHD were more likely hospitalized within 1 year (Table 2). In multivariable analyses, patients with IHD were more likely to die within 1 year compared to patients without IHD (hazard ratio [HR]: 1.12; 95% confidence interval [CI]: 1.03-1.21). Patients with IHD were more likely to die from CV causes compared to those without (HR: 1.21; 9%CI 1.09-1.35, Table 3). No significant association with non-CV mortality was observed (Table 3). After correction for the MAGGIC risk score, IHD was significantly associated with CV death (HR 1.14; 95%CI 1.03-1.27; P= 0.012), but not with all-cause (P=0.129) or non-CV death (P=0.733). Patients with IHD were more likely re-hospitalized for

HF (23% vs 21%) despite the competing risk of higher all-cause death. In total, 734 (4%) patients had new onset coronary artery disease (CAD) during follow-up, which was more common in patients with IHD (557, 6%) than without IHD (177, 2%, Table 2).

Patients with a history of IHD alone (HR: 1.12; 95%CI 1.03-1.22, P=0.01), but not new-onset IHD (HR: 0.96; 95%CI 0.84-1.09, P=0.489) had worse 1-year all-cause mortality after correcting for the MAGGIC risk score (Supplementary table 7). The association between a history of IHD alone and CV death remained significant (HR: 1.19; 95%CI 1.07-1.32, P=0.002). The association between new onset IHD and CV death was not significant (P= 0.563) after correction for the MAGGIC risk score.

We found an interaction between HF subtype (HFrEF; HFmrEF; HFpEF) and IHD status for 1-year mortality ($P_{interaction}$ <0.001), such that IHD was associated with higher mortality in patients with HFrEF (HR 1.20; 95%CI 1.05-1.36, P=0.006), but not with HFpEF (HR 0.95; 95%CI 0.77-1.16, P=0.592, Supplementary table 8). The interaction remained significant after correction for the MAGGIC risk score ($P_{interaction}$ <0.001). When restricting the test for interaction to patients with LVEF measured during the index hospitalization, significance remained ($P_{interaction}$<0.001). Finally, after correcting for treatment indication bias, being on β-blockers, statins and aspirin at discharge were associated with reduction in mortality in patients with IHD (Supplementary table 9).

Discussion.

In the largest global cohort of patients with acute HF to date, 52% of patients admitted for AHF had IHD, and 14% were admitted with new onset IHD. IHD was more common in lower income

countries, particularly eastern Europe and southeast Asia. Patients from countries with lower healthcare expenditure, and patients without health insurance were more often undertreated, and less likely underwent cardiac revascularization. Finally, IHD was associated with worse post-discharge mortality, especially in HFrEF. These data highlight the increasing burden of IHD in patients hospitalized for AHF from lower income regions and suggest that efforts to improve quality of treatment are warranted.

In REPORT-HF there was substantial regional variation in prevalence of IHD, which was most common in Southeast Asia, and Eastern Europe. Many of the countries included in these regions are currently undergoing rapid economic development, and population growth. Indeed, the age-standardized death-rate due to IHD is increasing in many locations across South, East, and Southeastern Asia, including China and India[14]. This also holds true for patients with HF—CAD was present in 54% of Indian patients and up to 50% of Chinese patients in the ASIAN-HF registry[15]. In INTER-CHF, IHD was present in 46% of Indians, 56% of Southeast Asians and 45% of patients from China[6]. While REPORT-HF included few countries from the Middle East, in the Gulf CARE registry CAD was the primary etiology in more than half of patients admitted for AHF[16], and in Pakistan up to 77% of patients have IHD[17]. Changing lifestyles, rapid economic development, and a higher exposure to risk factors including air pollution, high-fat diet, tobacco smoking, and excessive alcohol use might partially explain these findings. While no data was available in REPORT-HF on countries from sub-Saharan Africa, hypertensive heart disease was more common than IHD in INTER-CHF and THESUS-HF[6,18]. Results of the present study are best valued in light of the sampling strategy of REPORT-HF. The number of centers per country took into account the size of its population. However, priority was given to sites that could provide high-quality data, with little missingness. Given the limitations of performing

these large-scale cohort studies, especially in countries with heterogenous healthcare systems; our data likely represent a best-case scenario for many countries. This might introduce selection bias, and underestimate broader deficiencies in IHD care.

Evidence on in support of the association between economic factors and measures of treatment quality and use in CV disease (CVD) is substantial[19–21]. In the PURE study, use of aspirin, statins, ACEi/ARBs, β-blockers and anti-platelets decreased with a decrease of country level GDP in patients at high risk for CVD[21]. In the ASIAN-HF and INTER-CHF studies, use of ACEi/ARBs, β-blockers and MRAs was lower in lower income countries[6,22]. CABG/PCI during the index hospitalization was less common among patients without health insurance and patients from countries with low healthcare expenditure. Surprisingly, lower health care spending was associated with higher use of P2Y12 inhibitors, which was not explained by differences in healthcare facilities. The patent on clopidogrel expired in 2012[23], opened up the market up to cheaper generic versions. This is combined with fewer coronary revascularizations, which might lead to preferring medical treatment over interventions, however this deserves further study. Together, this highlights the importance of socio-economic factors in determining treatment of IHD.

IHD was associated with worse 1-year mortality, especially in patients with HFrEF. This confirms earlier results from several large registries and post-hoc analyses of randomized clinical trials[1–3]. The reoccurrence of MI/ACS within 1-year was low in REPORT-HF with less than 1% of patients without reporting a new MI/ACS during 1-year follow-up and only 2% of patients with IHD. This might be partially explained by underreporting of participants and/or investigators. Furthermore, these events were not adjudicated. In the SWEDE-HF registry, IHD was associated with an equally high risk for new IHD events across ejection fraction subtypes.

However, IHD conferred a higher risk for all-cause mortality in patients with HFrEF compared to patients with HFpEF[1]. In the Framingham Heart Study, IHD was associated with worse outcomes in patients with HFrEF compared to HFpEF[24]. We found a similar interaction between left ventricular (LV) subtype and IHD for CV-mortality, such that IHD was associated with a lower relative risk for CV death in patients with HFpEF compared to patients with HFrEF. This difference might be explained by the differences in proportion of deaths attributable to CV causes in patients with HFpEF and HFpEF[1]. Notably, this highlights a possible divergent role of IHD in patients with HFrEF and HFpEF, such that in patients with HFrEF, IHD might be a direct cause of ischemic LV dysfunction and myocardial cell loss, whereas in HFpEF, IHD plays a more complex role involving other comorbidities and mechanisms mediated by coronary microvascular and diastolic dyfunction[25].

Limitations

REPORT-HF reflects real world practice and shows differences in practice determined by locally available resources. For practical reasons, we did not take a random sample of countries or of clinical sites within a country. This may have led to possible selection bias regarding centers included in this study. Patients in lower income countries with IHD might be less likely to make it to hospital, which can cause survival bias in the inclusion of participants. Values for plasma natriuretic peptides were not available in a large number of patients and were not included in our multivariable models. Because the aim of REPORT-HF was to study differences in healthcare practices and treatment for AHF, diagnosis of AHF was made at the discretion of the local investigator and measurement of natriuretic peptides were not mandated. Patients had to provide informed consent, which potentially might select more stable patients and might explain the low index-hospitalization mortality. Hence, investigators might not have enrolled sicker, frailer

patients. Because ethnicity and region were largely colinear in REPORT-HF, we could not include both variables in our prediction models. In NA, many of the sites chosen served predominantly African-American patients, who develop HF at a younger age and have worse prognosis compared to patients of European descent. While this is the largest global study on acute HF to date, REPORT-HF did not include patients from sub-Saharan Africa, and the global proportion of Black patients is therefore relatively low. Data in REPORT-HF might not be reflective of populations seen in predominant rural facilities and the rural poor, especially in sub-Saharan Africa Time to hospitalization and recurrent ischemic events was not available, and thus we could not correct for the competing risk of mortality. Lastly, outcomes, cause of death and cause of hospitalization were determined by the investigator and were not independently adjudicated.

Conclusion.

IHD is common in patients hospitalized with AHF. The burden of IHD is greatest in patients from Eastern Europe and Southeast Asia. IHD in patients with AHF was associated with a higher 1-year mortality, especially in patients with HFrEF, regardless of region. Despite greater mortality, patients with IHD from regions with lower healthcare expenditure, and patients without health insurance were less likely treated with β-blockers and PCI/CABG. Initiatives are required to improve the implementation of life-saving therapies globally, especially in vulnerable patient-groups in low-income countries.

Clinical perspectives

The prevalence of IHD among patients hospitalized for HF is greater in lower compared to higher income countries and associated with worse outcomes, yet patients in countries with

lower healthcare expenditure per capita and patients without health insurance were less likely to undergo coronary revascularization or be prescribed anticoagulants.

Translational outlook:

Patients with HF in regions with the greatest burden of IHD are more commonly undertreated. These data highlight the need for initiatives to improve the implementation of life-saving therapies globally, especially in low-income countries.

References

1 Vedin O, Lam CSP, Koh AS, et al. Significance of Ischemic Heart Disease in Patients with Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. Circ Hear Fail 2017; **10**: e003875.

2 Badar AA, Perez-Moreno AC, Jhund PS, et al. Relationship between angina pectoris and outcomes in patients with heart failure and reduced ejection fraction: An analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Eur. Heart J. 2014; **35**: 3426–33.

3 Purek L, Laule-Kilian K, Christ A, et al. Coronary artery disease and outcome in acute congestive heart failure. Heart 2006; **92**: 598–602.

4 Yusuf S, Islam S, Chow CK, et al. 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**: 1231–43.

5 Kruk ME, Gage AD, Arsenault C, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. Lancet Glob. Heal. 2018; **6**: e1196–252.

6 Dokainish H, Teo K, Zhu J, et al. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Heal 2017; **5**: e665–72.

7 Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: Regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013; **15**: 808–17.

8 Filippatos G, Khan SS, Ambrosy AP, et al. International REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF): Rationale for and design of a global registry. Eur J Heart Fail 2015; **17**: 527–33.

9 Tromp J, Bamadhaj S, Cleland JGF, et al. 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**: e411–22.

10 Filippatos G, Angermann CE, Cleland JGF, et al. Global Differences in Characteristics, Precipitants, and Initial Management of Patients Presenting with Acute Heart Failure. JAMA Cardiol 2020; **5**: 401–10.

11 Ponikowski P, Voors AA, Anker SD, 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 . Eur J Heart Fail 2016; **18**: 891–975.

12 Pocock SJ, Ariti CA, McMurray JJV, et al. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. Eur Heart J 2013; **34**: 1404–13.

13 Tibshirani R, Bien J, Friedman J, et al. Strong rules for discarding predictors in lasso-type problems. J R Stat Soc Ser B Stat Methodol 2012; **74**: 245–66.

14 Burden G, Roth GA, Mensah GA, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol 2020; **76**: 2982–3021.

15 Lam CSP, Teng T-HK, Tay WT, et al. Regional and ethnic differences among patients

with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. Eur Heart J 2016; **37**: 3141–53.

16 Sulaiman K, Panduranga P, Al-Zakwani I, et al. Clinical characteristics, management, and outcomes of acute heart failure patients: Observations from the Gulf acute heart failure registry (Gulf CARE). Eur J Heart Fail 2015; **17**: 374–84.

17 Pillai HS, Ganapathi S. Heart Failure in South Asia. Curr Cardiol Rev 2013; **9**: 102–11.

18 Damasceno A, Mayosi BM, Sani M, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: Results of the sub-Saharan Africa survey of heart failure. Arch Intern Med 2012; **172**: 1386–94.

19 MacDonald MR, Tay WT, Teng THK, et al. Regional Variation of Mortality in Heart Failure With Reduced and Preserved Ejection Fraction Across Asia: Outcomes in the ASIAN-HF Registry. J Am Heart Assoc 2020; **9**: e012199.

20 Dewan P, Rørth R, Jhund PS, et al. Income Inequality and Outcomes in Heart Failure: A Global Between-Country Analysis. JACC Hear Fail 2019; **7**: 336–46.

21 Murphy A, Palafox B, O'Donnell O, 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**: e292–301.

22 Teng THK, Tromp J, Tay WT, et al. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. Lancet Glob Heal 2018; **6**: e1008–18.

23 United States Patent and Trademark Office. Extension Under 35 U.S.C. 156(e)(1) - OG

Date: 29 July 2003. https://www.uspto.gov/web/offices/com/sol/og/2003/week30/patxten.htm (accessed Dec 14, 2020).

24 Lee DS, Gona P, Albano I, et al. A systematic assessment of causes of death after heart failure onset in the community. Circ Hear Fail 2011; **4**: 36–43.

25 Tromp J, Ferreira JP, Janwanishstaporn S, et al. Heart failure around the world. Eur J Heart Fail 2019; **21**: 1187–96.

Figure legends.

Figure 1: A: Bar chart showing the proportion of patients with IHD undergoing a procedure (PCI/CABG) during the index hospitalization and medical therapy received at discharged stratified to tertiles of country healthcare expenditure. B: bar chart showing the proportion of patients with IHD undergoing procedures (PCI, CABG) during the index hospitalization and receiving medical therapy at discharge according to insurance status.

Figure 2: A: Kaplan Meier curve showing the cumulative mortality within one year stratified to ischemic heart disease status. B: cumulative incidence curve showing cardiovascular mortality within one year stratified to ischemic heart disease status.

Central illustration: World map showing the prevalence of ischemic heart disease per country included in REPORT-HF.

Table 1: baseline characteristics

Table 1. Baseline Characteristics	**No IHD**	**IHD**	
	8766	**9773**	**P-value**
Demographics			
Age (years)	65 (53, 76)	69 (60, 77)	<0.001
Men, n (%)	4861 (55%)	6505 (67%)	<0.001
Race, n (%)			<0.001
Caucasian	4377 (50%)	5270 (54%)	
Black	524 (6%)	342 (3%)	
Asian	2517 (29%)	3218 (33%)	
Native American	271 (3%)	104 (1%)	
Pacific Islander	5 (<1%)	2 (<1%)	
Other	1072 (12%)	837 (9%)	
Region, n (%)			<0.001
Central and South America	1655 (19%)	985 (10%)	
Eastern Europe	999 (11%)	1803 (18%)	
Eastern Mediterranean region and Africa	966 (11%)	1274 (13%)	
North America	810 (9%)	781 (8%)	
Southeast Asia	1006 (11%)	1321 (14%)	
Western Europe	1837 (21%)	1749 (18%)	
Western Pacific	1493 (17%)	1860 (19%)	
New Onset HF, n (%)	4090 (47%)	3805 (39%)	<0.001
Decompensated chronic HF, n (%)	4676 (53%)	5968 (61%)	
NYHA Class at prior to admission, n (%)			<0.001
I	408 (5%)	443 (5%)	
II	1525 (17%)	1754 (18%)	
III	2298 (26%)	2780 (28%)	
IV	956 (11%)	1196 (12%)	

LVEF, n (%)			<0.001
<40% (HFrEF)	3958 (45%)	4941 (51%)	
40-49% (HFmrEF)	1128 (13%)	1742 (18%)	
≥50% (HFpEF)	2867 (33%)	2296 (23%)	
Unknown	813 (9%)	794 (8%)	
Heart rate (bpm)	90 (75, 106)	84 (72, 100)	<0.001
Systolic blood pressure (mmHg, IQR)	130 (110, 150)	130 (114, 150)	<0.001
Diastolic blood pressure (mmHg, IQR)	80 (69, 90)	80 (69, 90)	0.014
Signs and symptoms			
Dyspnea at rest, n (%)	6324 (83%)	7278 (83%)	0.64
Orthopnea, n (%)	5343 (78%)	6281 (78%)	0.93
Chest pain, n (%)	3152 (41%)	4918 (56%)	
Peripheral edema, n (%)	5510 (71%)	5891 (67%)	<0.001
Pulmonary Rales, n (%)	4676 (66%)	5604 (68%)	0.006
Medical history			
Hypertension, n (%)	5063 (58%)	6745 (69%)	<0.001
Atrial fibrillation/flutter, n (%)	3049 (35%)	2717 (28%)	<0.001
COPD/Asthma, n (%)	1179 (13%)	1476 (15%)	0.001
Anemia, n (%)	3785 (43%)	4939 (51%)	<0.001
Valvular Heart Disease, n (%)	2228 (25%)	1451 (15%)	<0.001
Diabetes, n (%)	2538 (29%)	4527 (46%)	<0.001
Chronic Kidney Disease, n (%)	1452 (17%)	2314 (24%)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; 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; IHD, ischemic heart disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2: in-hospital characteristics and 1-year outcomes

Table 2: hospital characteristics	**No IHD**	**IHD**	
			P-value
Mode of transport, n (%)			<0.001
Own transport	6077 (69%)	6317 (65%)	
Ambulance	2046 (23%)	2739 (28%)	
Other	637 (7%)	709 (7%)	
Hospital Point of Entry			
Point of Entry, n (%)			<0.001
Emergency Room	5680 (65%)	5947 (61%)	
Heart Failure Facilities	422 (5%)	501 (5%)	
Cardiac Ward	1513 (17%)	1833 (19%)	
Cardiac/ Coronary ICU	559 (6%)	893 (9%)	
General/ Medical/ Surgical ICU	266 (3%)	216 (2%)	
Other	320 (4%)	378 (4%)	
Time to treatment for AHF			
Time to any (minutes)	60 (13, 185)	53 (8, 168)	<0.001
Time to I.V. vasodilators (minutes)	77 (25, 255)	58 (11, 202)	<0.001
Time to I.V. inotropics (minutes)	230 (45, 1728)	233 (42, 2558)	0.540
Time to I.V. diuretics (minutes)	78 (22, 224)	69 (15, 219)	<0.001
Discharge Medication, n (%)			
ACEi/ARB, n (%)	5604 (66%)	6280 (66%)	0.620
GRT, n (%)	5156 (92%)	5708 (91%)	0.030
Median Fraction (IQR)	0.5 (0.25-0.63)	0.33 (0.25-0.57)	0.001
Beta-blockers, n (%)	5971 (70%)	7063 (74%)	<0.001
GRT, n (%)	5805 (97%)	6937 (98%)	<0.001
Median Fraction (IQR)	0.25 (0.20-0.50)	0.25 (0.13-0.50)	0.052

MRA, n (%)	4247 (50%)	4599 (48%)	0.057
Median Fraction (IQR)	0.33 (0.33-0.5)	0.33 (0.33-0.67)	<0.001
Length of stay (Days)	8 (5, 12)	8 (5, 12)	<0.001
1-year outcomes[1]			
Mortality, n (%)	1500 (18%)	1958 (21%)	<0.001
Hospitalization, n (%)	2997 (36%)	3671 (39%)	<0.001
Days in hospital	11 (5, 23)	11 (5, 22)	0.95
Hospitalization for HF, n (%)	1769 (21%)	2168 (23%)	0.002
Days in hospital	10 (5, 20)	10 (5, 20)	0.88
CAD, n (%)	177 (2%)	557 (6%)	<0.001
MI/ACS, n (%)	46 (<1%)	144 (2%)	<0.001
CABG, n (%)	31 (<1%)	117 (1%)	<0.001
PCI, n (%)	84 (1%)	322 (3%)	<0.001

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; GRT, guideline recommended therapy; PCI, percutaneous coronary intervention.

[1]patient population not lost to follow-up within one year used as denominator.

Table 3: Cox regression analyses

All-cause death		
Strata	No IHD	IHD
Cases/N	1500/8301	1958/9317
Events/100 patient-years (95%CI)	20.3 (19.3-21.4)	24.1 (23.0-25.2)
Univariable	ref	1.18 (1.09-1.29) <0.001
Model 1		1.10 (1.01-1.20) 0.028
Model 2	ref	1.08 (0.99-1.18) 0.060
Model 3	ref	1.12 (1.03-1.21) 0.010
MAGGIC risk score	ref	1.06 7 (0.98-1.16) 0.129
CV death		
Cases/N	870/8301	1205/9317
Events/100 patient-years (95%CI)	11.8 (11.0-12.6)	14.8 (14.0-15.7)
	HR (95%CI) p-value	
Univariable	ref	1.25 (1.13-1.39) <0.001
Model 1	ref	1.22 (1.09-1.36) <0.001
Model 2	ref	1.17 (1.05-1.30) 0.004
Model 3	ref	1.21 (1.09-1.35) <0.001
MAGGIC risk score	ref	1.14 (1.03-1.27) 0.012
Non-CV death		
Cases/N	235/8301	284/9317
Events/100 patient-years (95%CI)	3.2 (2.8-3.6)	3.5 (3.1-3.9)
	HR (95%CI) p-value	
Univariable	ref	1.08 (0.90-1.29) 0.417
Model 1	ref	0.93 (0.78-1.12) 0.452
Model 2	ref	0.97 (0.81-1.17) 0.787
Model 3	ref	1.17 (0.84-1.62) 0.346
MAGGIC risk score	ref	0.97 (0.81-1.16) 0.733

Abbreviations: CV, cardiovascular

Model 1: Age, sex, history of hypertension; atrial fibrillation; anemia; valvular heart disease

Model 2: Model 1 + region, and heart failure diagnosis (new onset versus decompensated chronic heart failure)

Model 3: Model 3 + treatment with ACEi/ARBs, MRAs, beta-blockers and MRAs at discharge

MAGGIC risk score: Left ventricular ejection fraction, systolic blood pressure, age, sex, body mass index, creatinine, New York Heart Association class, history of diabetes or COPD, time since diagnosis, use of ACEi/ARBs at discharge, use of beta-blockers at discharge.