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REVIEW

Heart failure around the world

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With increasingly large sample sizes required to demonstrate event reduction, heart failure outcome trials are no longer being performed in a small group of selected patients and countries, but at a global scale with worldwide contribution of patients from countries with considerable differences in background therapy, socioeconomic status and healthcare practices. Recent studies have highlighted how socioeconomic determinants rather than geographical factors may underlie the heterogeneity of patient populations across the globe. Therefore, in this review, we evaluated (i) regional differences in patient characteristics and outcomes in recent epidemiologic studies; (ii) regional differences in worldwide representativeness of clinical trial populations; and (iii) the role of socioeconomic determinants in driving country differences in heart failure trial enrolment and clinical outcomes.

Keywords Heart failure • Geographic differences • Outcome • Socioeconomic status

Introduction

Therapeutic advances in the treatment of heart failure (HF) with reduced ejection fraction (HFrEF) made necessary to recruit more patients in increasingly large sample sizes to demonstrate event reduction with novel therapies on top of the evolving current standard of care. Recent experience has shown that relying on selected countries, particularly those from North America (NA) and Western Europe (WE), to provide the requisite number of sites and patients will not suffice, as recruitment of patients from these countries into clinical trials has become increasingly problematic. As a result, HF outcome trials can no longer be performed in a small group of selected countries, and recent trials have included several thousands of patients with worldwide contribution.[1] Data from the European Medicines Agency showed that the Middle-East/Asia-Pacific (AP) region, excluding Australia and New Zealand, contributed 2.0% of patients in pivotal trials in 2005, rising to 12.8% in 2011, in sharp contrast to a decreasing percentage in WE and NA during the same period.[2] Paradoxically the non-US countries have been called 'rest of the world' in prior publications,[3,4] when they should perhaps be more appropriately considered 'most of the world'.

The number of countries included in global HF trials has grown considerably over time – the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) study enrolled patients from three countries,[5] while the recent Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) and Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) trials enrolled patients from 48 and 32 countries, respectively.[6,7] An increasing proportion of recruited patients come from Eastern Europe (EE) and the AP region.[8–10]

Recent publications have highlighted patients' features outside clinical trials. Results from global HF registries, including the International Congestive Heart Failure (INTER-CHF) study and the Asian Sudden Cardiac Death in Heart Failure registry (ASIAN-HF), have led to a greater appreciation of regional differences in HF populations. The pending results of the International Registry to assess mEdical Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF) and Global Congestive Heart Failure (G-CHF, ClinicalTrials.gov Identifier: NCT03078166) registry will add to these contemporary insights.[11–16] These recent global registry data allow assessment of the representativeness of trial populations to their respective regional registry populations. While ethnicity and geographic location likely play a role in regional

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differences, other factors such as regional income level, access to healthcare, out-of-pocket cost for hospitalization and wealth distribution are almost certainly also involved. These socioeconomic determinants have an important impact on cardiovascular outcomes, and are likely to be responsible also for driving varying enrolment rates, quality of care and clinical outcomes across different countries.[17,18]

Therefore, in this review, we will evaluate (i) regional differences in patient characteristics and outcomes in recent epidemiologic studies; (ii) regional differences in representativeness of clinical trial populations; and (iii) the role of socioeconomic determinants in driving worldwide differences in HF trial enrolment and clinical outcomes.

Regional differences in heart failure

Overall clinical characteristics

There are considerable regional differences in patient characteristics reported in global clinical registries and trials.[19] In the following sections, we focused on studies published after 2010 to reduce time-lag and increase comparability between studies and registries (*Tables 1–3*).[8,11,13,20–34] In the PARADIGM-HF trial, patients from AP were almost a decade younger compared to patients from NA and WE.[8] This is in line with recent reports of the ASIAN-HF registry and signifies a potentially shifting burden of HF from NA, WE and EE to the AP region.[12,35,36] Yet despite their relative youth, Asian patients have a strikingly high prevalence of co-morbidities.[12,13,37] There are also important within-region differences that are often not considered. For instance, within Asia, Southeast Asian patients have the highest burden of risk factors and worse outcomes compared to Northeast and South Asian patients, possible due to a rapid epidemiologic transition.[12,13,38] Furthermore, Southeast Asia is home to a unique lean diabetic HF with preserved ejection fraction (HFpEF) phenotype.[13,39] Similar to what has been observed in Asia, patients enrolled in clinical trials from Latin America (LA) are considerably younger, but in contrast to the Asian patients, they have a lower burden of co-morbidities.[40] An important and locally unique cause of HF in LA is Chagas disease,[41] which is associated with worse clinical outcomes compared to other aetiologies of HF.[41] There is limited data from Africa; however the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) and INTER-CHF studies have reported that hypertensive heart disease is an important risk factor for developing HF in Africa.[11,42] Furthermore, peripartum cardiomyopathy appears to be a more common cause of HF in sub-Saharan Africa than in other regions around the world.[43]

Heart failure with reduced ejection fraction therapies and outcomes

Regional differences are also apparent in treatment and quality of care.[8,11,20,24,44] Results from the Change the Management of Patients with Heart Failure (CHAMP-HF) registry showed

Table 1 Characteristics of ambulant patients with heart failure with reduced ejection fraction stratified according to trial vs. registry and geographic region

	Trial					Registries											
	PARADIGM-HF[8]					ESC-HF-LT[20]		Olmsted[21]	IMPROVE-HF[22]		CHAMP-HF[23]		ASIAN-HF[24]		INTER-CHF[11]	
	EE	WE	NA	AP	LA	EE	WE	NA	NA		NA		AP		LA	
Patients (*n*)	2762	1680	602	1487	1433	1290	514	265	15 177		3497		5276		869	
Age (years)	65	68	65	58	58	64	62	72	68		66		60		67	
Male sex (%)	77	82	83	80	73	73	73	57	71		71		78		61	
Ischaemic aetiology (%)	70	58	63	58	43	47[a]	33	N/A	65		40		50		25	
DM (%)	34	36	49	35	27	31	22	28	34		41		40		21	
ACEi/ARB (%)	N/A	N/A	N/A	N/A	N/A	90	93	N/A	78		61		77		76	
Beta-blockers (%)	95	94	97	89	92	91	92	N/A	86		67		79		73	
ICD (%)	7	33	54	2	4	14	21	N/A	49		N/A		12		N/A	
Mortality per 100 py	8 (8–9)	7 (6–8)	8 (7–10)	9 (8–10)	10 (9–11)	8[a]	8[a]	20[a]	N/A		N/A		12 (11–13)		9[a]	
HF hospitalizations per 100 py	7 (7–8)	7 (6–7)	11 (9–13)	7 (7–8)	5 (5–6)	13[a]	16[a]	N/A	N/A		N/A		15 (14–16)		N/A	

ACEi, angiotensin-converting enzyme inhibitor; AP, Asia-Pacific; ARB, angiotensin receptor blocker; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure registry; CHAMP-HF, Change the Management of Patients with Heart Failure; DM diabetes mellitus; EE, Eastern Europe; ESC-HF-LT, European Society of Cardiology Heart Failure Long-Term Registry; HF, heart failure; ICD, implantable cardioverter-defibrillator; IMPROVE-HF, Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; INTER-CHF, International Congestive Heart Failure; LA, Latin America; N/A, not available; NA, North America; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; py, patient-years; WE, Western Europe.
[a]Percentage all-cause mortality at 1 year.

Table 2 Characteristics of ambulant patients with heart failure with preserved ejection fraction stratified according to trial vs. registry and geographic region

	Trials							Registries			
	PARAGON-HF[25]					TOPCAT[26]		Swede-xHF[27]	Olmsted[21]	FHS[28]	ASIAN-HF[13]
	EE	WE	NA	AP	LA	Americas	EE	WE	NA	NA	AP
Patients (*n*)	1804	1327	560	761	370	1767	1678	6488	291	326	1204
Age (years)	71	76	74	72	72	72	66	77	78	82	68
Male sex (%)	48	48	53	50	40	50	47	45	37	34	50
Atrial fibrillation (%)	51	58	58	45	36	42	28	61	N/A	38	29
Hypertension (%)	98	94	97	91	96	N/A	N/A	81	89	62	71
DM (%)	45	38	49	44	38	45	20	30	32	20	45
Mortality per 100 py	N/A	N/A	N/A	N/A	N/A	7.1	2.1	N/A	N/A	N/A	6 (5–8)
HF hospitalizations per 100 py	N/A	N/A	N/A	N/A	N/A	8.8	0.8	N/A	N/A	N/A	9 (7–11)

AP, Asia-Pacific; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure registry; DM, diabetes mellitus; EE, Eastern Europe; FHS, Framingham Heart Study; HF, heart failure; LA, Latin America; N/A, not available; NA, North America; PARAGON-HF, Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF; py, patient-years; Swede-HF, Swedish Heart Failure registry; TOPCAT, Treatment of Preserved Cardiac Function with an Aldosterone Antagonist; WE, Western Europe.

Table 3 Characteristics of acute heart failure patients according to trial vs. registry and geographic region

	Trials													Registries				
	ASCEND-HF[29]					PROTECT[30]			ASTRONAUT[31]					ESC-HF-LT[20]		ADHERE[32]	GWTG[33]	ADHERE-AP[34]
	EE	WE	NA	AP	LA	EE	WE	NA	EE	WE	NA	AP	LA	EE	WE	NA	NA	AP
Patients (*n*)	967	504	3243	1762	665	676	388	313	495	395	123	439	163	1429	242	105 388	40 239	10 171
Age (years)	69	74	67	67	70	71	75	68	65	69	59	61	65	69	74	72	80	67
Male sex (%)	69	67	65	65	60	68	70	74	77	80	76	77	72	62	60	48	46	57
CAD (%)	67	53	60	60	32	N/A	N/A	N/A	61	55	52	57	28	N/A	N/A	57	51	50
DM (%)	29	43	49	49	34	43	49	53	45	45	53	43	33	37	30	44	39	45
LOS (days)	10	8	5	5	6	8 (15)[a]	10	5	11	10	5	5	6	N/A	N/A	4	N/A	6
Loop diuretic dose (mg)	40	60	80	40	40	200 (80)[a]	380	400	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mortality 180 days (%)	9	15	13	12	17	19 (12)[a]	20	20	10	9	3	17	9	N/A	N/A	9.8[b]	N/A	N/A

ADHERE, Acute Decompensated HEart Failure National Registry; AP, Asia-Pacific; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; ASTRONAUT, Aliskiren Trial on Acute Heart Failure Outcomes; CAD, coronary artery disease; DM, diabetes mellitus; EE, Eastern Europe; ESC-HF-LT, European Society of Cardiology Heart Failure Long-Term Registry; GWTG, Get With The Guidelines; LA, Latin America; LOS, length of stay; N/A, not available; NA, North America; PROTECT, Placebo-controlled Randomized study of the selective A_1 adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal funcTion; WE, Western Europe.

[a]Between brackets signified numbers for Russia.

[b]60–90 day all-cause mortality.

that among eligible patients, 61%, 67%, and 33% were only prescribed angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor antagonist (MRA) therapy, respectively.[45] In Asia, ACE inhibitors/ARBs and beta-blockers were prescribed in 77% and 79% of eligible patients, respectively[24] (*Table 1*). This percentage was considerably higher in Europe, were registry data showed that 90–92% of patients were on ACE inhibitors/ARBs/beta-blockers, yet only 50% of patients were on MRAs.[20] However, results from the CHAMP-HF registry, ASIAN-HF registry and European systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) study, show that these key drugs are often underdosed, especially in Asia.[24,45,46] The largest regional differences in treatment are seen in device usage.[8,10] In the PARADIGM-HF trial, implantable cardioverter-defibrillators (ICDs) were used in 33% and 54% of patients from WE and NA, respectively, yet despite similar guideline recommendations, ICDs were only used in 7% of patients from EE, 2% of patients from AP and 4% of patients from LA.[8] In addition, advanced HF therapies, including left ventricular assist devices and heart transplantation, are still very limited in most low-middle-income countries compared to WE and NA.[47,48] This difference is likely related to differences in reimbursement; a separate study from ASIAN-HF showed that on a country level, there was a strong association between device usage and out-of-pocket pay.[49]

Significant differences in mortality were seen in the PARADIGM-HF trial; patients from LA [10 (95% confidence interval-CI 9–11) deaths per 100 patient-years] and AP [9 (95% CI 8–10) deaths per 100 patient-years] had worse mortality compared to WE [7 (95% CI 6–8) deaths per 100 patient-years] independent of differences in clinical characteristics (*Table 1*).[8] Regional variations in clinical outcome are more pronounced when looking at hospitalization for HF.[8–10] HF hospitalization rates were highest in patients from NA [11 (95% CI 9–13) HF hospitalizations per 100 patient-years] and lowest in patients from LA [5 (95% CI 5–6) HF hospitalizations per 100 patient-years].[8] Data from ASIAN-HF showed that 6-month mortality is high in Asia at 6.9% and highest in Southeast Asia at almost 9%.[12]

Heart failure with preserved ejection fraction outcomes

Regional differences in clinical outcomes were most pronounced in the Treatment of Preserved Cardiac Function with an Aldosterone Antagonist (TOPCAT) trial, where mortality rates of participants from Russia/Georgia were similar to the event rates of the general population.[10] Moreover, many of the participants from Russia/Georgia in the TOPCAT trial did not receive/took the study drug despite being randomized to active treatment.[50]

In ASIAN-HF, 1-year mortality rates of patients with HFpEF from AP were 7%.[13] Importantly, there are within-region differences in clinical outcomes in Asia; patients with HFpEF from Southeast Asia were at a four-fold higher risk of mortality within 1 year compared to patients from East and South Asia.[13] These within-region differences were more pronounced in patients with HFpEF, than patients with HFrEF in ASIAN-HF. However, this could also be caused by the relatively lower regional subgroup numbers in the HFpEF cohort.[12,13]

Acute heart failure treatment and outcomes

There are important regional differences in length of stay (LOS) and treatment in acute HF (AHF)[11,29,31,51] (*Table 3*). In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, the LOS in EE was double the LOS observed in NA and AP.[29] Similar results were seen in the Placebo-controlled Randomized study of the selective A_1 adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal funcTion (PROTECT) and Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) trials, where LOS was considerably longer in patients from EE compared to NA and AP.[30,31] However, there are important within-region differences in LOS. For example, within the AP region median LOS is 6 days, but can go up to 21 days in countries such as Japan.[38,52] The daily loop diuretic dose seems to inversely track LOS; in the ASCEND-HF trial patients from EE received almost half the daily loop diuretic dose compared to patients from NA[29] (*Table 3*). In the PROTECT trial, patients in Russia received less than half of the daily loop diuretic dose compared to patients from WE and NA.[30]

There are also important regional differences in post-discharge outcomes of AHF patients. In the ASCEND-HF trial, patients from LA (17%) had the highest 180-day mortality rate, while patients from EE (9%) had the lowest mortality rates[29] (*Table 3*). In the ASTRONAUT trial, mortality rates were lowest in patients from NA (3%), while patients from the AP (17%) and EE (10%) regions had the highest mortality rates.[31] In contrast, mortality rates were highest in NA (20%) and WE (20%) in the PROTECT trial and lowest in Russia and Argentina.[30] Across trials and registries, rehospitalization rates show a more consistent pattern – rehospitalization rates are generally lower in patients from EE, LA and AP, compared to NA and WE.[29–31] Taken together, these data suggest important regional heterogeneity in post-discharge outcome of AHF.

Regional differences in representativeness of clinical trial populations

How representative are trial populations for their respective regions? Generally, patients qualifying for participation in clinical trials are younger and more often men. A study in the Euro Heart Survey on Heart Failure found that only 13% of patients qualified for participation in at least one of the selected trials (MERIT-HF, SOLVD and RALES) and these patients were younger and more often men.[53] Similar results were seen in the Swedish Heart Failure registry – younger men with an ischaemic aetiology of HF more frequently qualified for participation in the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine (SHIFT) trial.[54] In AHF, only 20% of patients in the Acute Decompensated HEart Failure National REgistry (ADHERE) in the United States

and AP met basic inclusion/exclusion criteria for the Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial.[55] The continued under-representation of older patients and women in HF trials has recently been highlighted.[56]

When comparing trial to registry data in specific regions, the greatest differences are found among patients from WE and NA[8,10–12,20,57,58] (*Tables 1–3*). Patients from NA and WE enrolled in ambulatory HFrEF, HFpEF and in AHF trials are younger and more often men compared to contemporary registries, while patients from the AP and EE regions were more similar to registry populations (*Tables 1–3*). A potential explanation may be the older age of patients from NA and WE, who may have more age-related co-morbidities that exclude them from trials, or who may be less keen to participate in randomized clinical trials. We further postulate that socioeconomic differences across regions may explain this disparity, as discussed below.

Socioeconomic determinants as drivers of enrolment and outcomes

Country differences may be attributable to differences in socioeconomic determinants rather than the geographic location *per se*. These include differences in country income level, inequality in income levels and out-of-pocket costs, which are major determinants of healthcare systems organizations, education level, access to and quality of care. While these are plausible drivers of what is often described as geographic differences, a limited number of studies have explored their influence on patient heterogeneity in trials and registries.[12,18,24,49,59,60]

Socioeconomic determinants driving enrolment of trials

The primary region of enrolment for almost half of contemporary HF trials lays outside WE and NA.[61] A meta-analysis of 300 trials showed that the proportion of trials having their primary region of enrolment in NA or WE decreased from almost 70% to just over 50% within a decade.[61] An important driver of this trend is the greater efficiency of trial enrolment (higher rate of enrolment per centre) in EE and LA.[30,31,61,62] In the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) programme, sites from LA (20 patients per site) and EE (20 patients per site) enrolled more than twice the number of patients per site than those from NA (seven patients per site) and WE (eight patients per site).[62] Similar differences were seen in the ASCEND-HF and ASTRONAUT trials[29,31] (*Figure 1*). The regional differences in recruitment rates do not appear to be explained by differences in trial eligibility by inclusion/exclusion criteria: for example, modelling the RELAX-AHF trial criteria in the ADHERE and ADHERE-AP registries showed that a similarly low proportion of patients with AHF in the US, LA, or AP were eligible.[55] Yet, when we order the regions according to compound income level, enrolment rates seem to show an inverse association (*Figure 1*). In many lower- and middle-income regions, which have high out-of-pocket costs, participation in trials is often the only means for access to medical care. This creates a potential ethical dilemma, where patients are forced into clinical trials out of deprivation. Moreover, the resulting medical products following a positive trial, will often be out of reach for the trial patients after trial termination. This might also provide for a potential explanation for the differences in representativeness of trial populations across regions. Beyond income level, other factors that may drive differential enrolment include cultural and language issues in relation to the informed consent process and documentation, as well as varying levels of stringency with scientific or regulatory review processes, patient protection rights or compensation for trial-related injury.[19,63]

Influence of socioeconomic determinants on patient characteristics, medication and outcomes

Socioeconomic determinants also influence patient characteristics and usage of medication. A recent study from the ASCEND-HF trial was the first in an AHF trial population to study the influence of country income in a trial population.[18] Patients from higher-income countries had lower rates of protocol completion, higher rates of adverse events, and similar mortality rates compared to lower- and middle-income countries.[18] The importance of socioeconomic status on access to medication, lifestyle, treatment quality and clinical outcomes is also apparent beyond HF, and was shown to be relevant in the treatment of stroke and secondary prevention of cardiovascular events in populations at risk.[64–66] For example, patients from low-income countries are more likely to be smokers, which might be an important opportunity for intervention.[11] Device usage also seems to be driven by socioeconomic determinants, with data from ASIAN-HF showing a strong association between underusage of devices in eligible patients with HFrEF and country income level as well as out-of-pocket costs.[49]

Access to care, directly influenced by out-of-pocket costs, also might drive reporting of endpoints in clinical trials. A case in point is India, which has one of the highest out-of-pocket costs for healthcare in the world ranging anywhere from 50% and upwards depending on the state.[67] The only country-level data form an ambulant HF trial available is from a post-hoc analysis from the PARADIGM-HF trial focusing on Asia; not surprisingly, among Asian countries in PARADIGM-HF the rate of HF hospitalizations was lowest in India (*Figure 2*).[68] Thus, endpoints such as HF hospitalizations and major vascular endpoints including revascularization and myocardial infarction, may not reflect the same severity of disease in countries with a high (vs. low) out-of-pocket cost. Similarly with signs and symptoms, there seems to be a disconnect between signs and symptoms and outcomes in lower-income regions may be in part due to differences between countries in the way patients are evaluated.

Other than regional income, the distribution of income as captured by the Gini coefficient might drive differences in patient characteristics and clinical outcomes.[69] In a recent pooled analysis of the Aliskiren Trial to Minimize OutcomeS in Patients with Heart Failure (ATMOSPHERE) and PARADIGM-HF trials, greater income inequality (higher Gini coefficient) predicted adverse outcomes

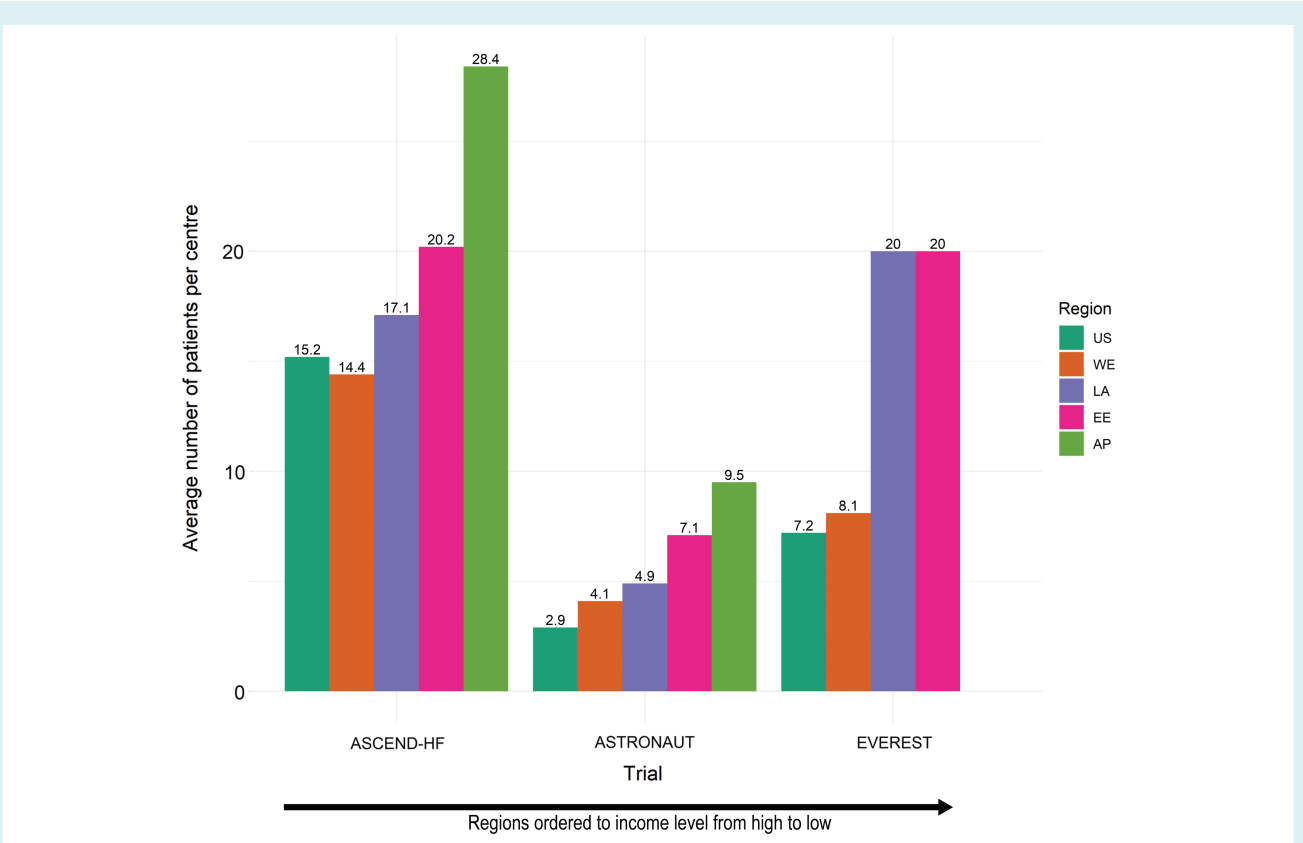

Figure 1 Enrolment per region, per trial, ordered by compound gross domestic product per region from high to low. AP, Asia-Pacific; EE, Eastern Europe; LA, Latin America; US, United States; WE, Western Europe.

with a similar impact as major co-morbidities.[69] Furthermore, unpublished data from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trials showed that both greater income inequality as well as lower country income were important drivers of adverse outcomes), with combined greater impact on death rates than any other co-morbid condition.[70–72]

While these previous studies have provided us with important new insights into how socioeconomic determinants might drive geographic differences, more data are needed. Several other important drivers such as the out-of-pocket pay, country level healthcare spending and hospital bed density warrant further attention. Future clinical trial should collect these socioeconomic factors to understand the regional differences in clinical characteristics and outcomes.

Implication of regional differences and recommendations

There are several important benefits and risks of global patient heterogeneity for clinical trials. Benefits include faster enrolment, with greater representation from patients with non-white ethnicity and the facilitation of generalizability of the results. Inherent risks include regional and socioeconomic differences in background therapy and patient characteristics. The clearest example illustrating the effects of differences in background therapy is from the Platelet Inhibition and Patient Outcomes (PLATO) trial, where ticagrelor compared to placebo was less effective in patients from NA[73]; an effect attributable to differences in background aspirin dosing wherein ticagrelor was most effective in patients on low aspirin maintenance dose.[74] Specifically for global HF clinical trials, newer therapies are often tested on top of optimal guideline-directed medical treatment for HF; yet the background HF medical therapy is known to vary by region,[24,45,46] with even greater variation in background HF device therapy.[49] At the very least, background therapy should be closely monitored by region during the conduct of global HF trials, with measures taken to close treatment gaps in specific regions as needed (e.g. additional reminders to/education of physicians regarding guideline-directed medications and doses).

Other recommendations to mitigate the trial risks related to regional differences include[9]: using objective measures of disease severity such as elevated natriuretic peptides measured at a core laboratory as inclusion criteria; auditing and independent adjudication of endpoints, where soft endpoints such as hospitalization

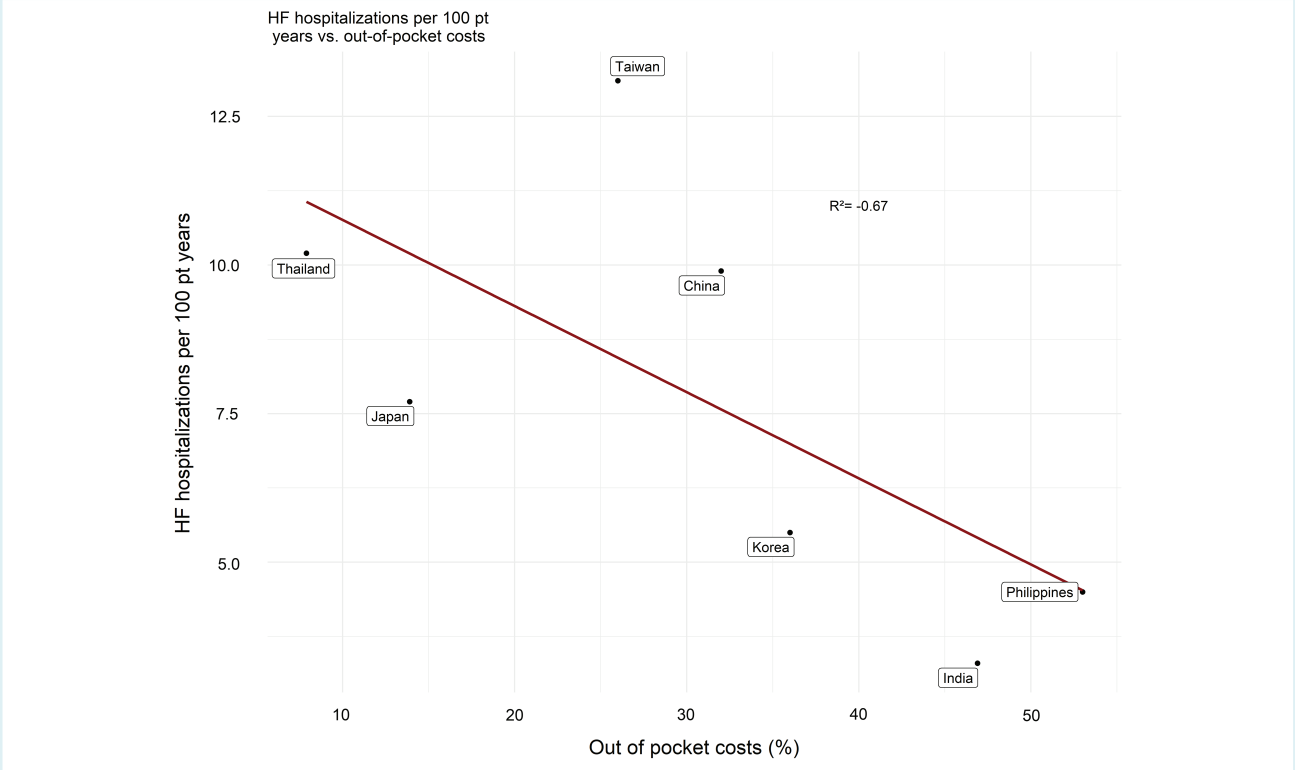

Figure 2 Association between heart failure (HF) hospitalizations per 100 patient-years and out-of-pocket costs in Asian countries from PARADIGM-HF. Based on data from.[68]

for HF are coupled with objective measures including response to diuretics and natriuretic peptides (*Table 4*). In addition, lessons from TOPCAT suggest that there is a need for conducting trials in a variety of geographic jurisdictions without letting one or a limited number of regions dominate enrolment. This should be combined with informing sites of planned regional interim analyses, which might lead to a lower regional cap if patient characteristics are considerably different. Since regional differences in patient characteristics and outcomes could ultimately affect the success of a clinical trial, the leadership of clinical trials including the Steering Committee and Data Safety Monitoring Committee should plan to be pro-active in their review of differences between various regions, Early recognition of trends that threaten the integrity of a trial could then lead to corrective action addressing issues of concern.[75]

Recent results from PARADIGM-HF and the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF (PARAGON-HF) have shown that the combined usage of natriuretic peptides and requirements with regards to background therapy can considerably reduce regional heterogeneity.[8,25] This is particularly striking in the PARAGON-HF trial, where regional differences are smaller compared to earlier HFpEF trials.[25] Having pre-specified regional caps provides an important 'check and balance' on the enrolment of patients, but in practice is not universally supported yet, particularly when there is great emphasis on rapid enrolment. However, the benefits of rapid enrolment should be weighed against the risks of over-representation of particular regions with rapid enrolment. Alternative trial designs such as an adaptive design, facilitate the introduction of changes in sample size and regional caps during interim analyses, and might

Table 4 Recommendations to mitigate the risk of regional heterogeneity for global heart failure trials

Trial design
• Consider an adaptive trial design
Inclusion criteria and outcomes
• Objective inclusion criteria (NPs, preferably measured at a core laboratory)
• Include inclusion criteria with regard to (optimal) background therapy
• Auditing and independent adjudication of endpoints
• Combining objective measures (NPs, response to diuretics) with soft endpoints such as HF hospitalization
Regional stratification
• Cap regional enrolment
• Early planned interim analysis for regional differences, with lowering of the regional cap if patient characteristics are divergent

HF, heart failure; NP, natriuretic peptide.

reduce the effects of regional heterogeneity. The use of adaptive trial designs has several additional benefits, including the possibility of sample size re-estimation, which can have considerable cost benefits. Nevertheless, trials with an adaptive design are under close regulatory scrutiny and require attention to operational procedures and statistical techniques used to reduce the type I error.[76]

Conclusion

Heart failure is a growing healthcare burden globally. Important regional differences exist in patient characteristics, HF aetiology and co-morbidity burden, where many patients from lower- and middle-income regions present at a considerably younger age compared to those from high income regions, and region-specific issues include lean diabetic HFpEF in Southeast Asia, Chagas disease in LA, as well as hypertensive heart disease and peripartum cardiomyopathy in Africa. Regional differences in usage of guideline-directed HF medical therapies, devices and outcomes have also been reported. Furthermore, there are important differences in trial population representativeness between regions, which are most apparent in NA and WE. Socioeconomic determinants such as country income level and out-of-pocket costs may affect country differences in both trial enrolment, trial population representativeness, patient characteristics and clinical outcomes. The full extent of the influence of socioeconomic determinants on presentation, management and outcomes of HF patients is not fully understood and presents an area where further investigation is urgently needed. Better recognition and understanding of the impact of regional differences in the characteristics, management and outcomes of patients with HF enrolled in clinical trials is essential in order to improve our ability to adequately test the safety and efficacy of novel therapies.

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