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ORIGINAL ARTICLE

Eligibility of Asian and European registry patients for phase III trials in heart failure with reduced ejection fraction

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Abstract

Aims Traditional approaches to designing clinical trials for heart failure (HF) have historically relied on expertise and past practices. However, the evolving landscape of healthcare, marked by the advent of novel data science applications and increased data availability, offers a compelling opportunity to transition towards a data-driven paradigm in trial design. This research aims to evaluate the scope and determinants of disparities between clinical trials and registries by leveraging natural language processing for the analysis of trial eligibility criteria. The findings contribute to the establishment of a robust design framework for guiding future HF trials.

Methods and results Interventional phase III trials registered for HF on ClinicalTrials.gov as of the end of 2021 were identified. Natural language processing was used to extract and structure the eligibility criteria for quantitative analysis. The most common criteria for HF with reduced ejection fraction (HFrEF) were applied to estimate patient eligibility as a proportion of registry patients in the ASIAN-HF (N = 4868) and BIOSTAT-CHF registries (N = 2545). Of the 375 phase III trials for HF, 163 HFrEF trials were identified. In these trials, the most frequently encountered inclusion criteria were New York Heart Association (NYHA) functional class (69%), worsening HF (23%), and natriuretic peptides (18%), whereas the most frequent comorbidity-based exclusion criteria were acute coronary syndrome (64%), renal disease (55%), and valvular heart disease (47%). On average, 20% of registry patients were eligible for HFrEF trials. Eligibility distributions did not differ (P = 0.18) between Asian [median eligibility 0.20, interquartile range (IQR) 0.08–0.43] and European registry populations (median 0.17, IQR 0.06–0.39). With time, HFrEF trials became more restrictive, where patient eligibility declined from 0.40 in 1985–2005 to 0.19 in 2016–2022 (P = 0.03). When frequency among trials is taken into consideration, the eligibility criteria that were most restrictive were prior myocardial infarction, NYHA class, age, and prior HF hospitalization.

Conclusions Based on 14 trial criteria, only one-fifth of registry patients were eligible for phase III HFrEF trials. Overall eligibility rates did not differ between the Asian and European patient cohorts.

Keywords Heart failure; Clinical trials; Patient eligibility; Disease registry; Generalizability

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†On behalf of the Asian-HF Investigators (see Appendix)

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Introduction

The eligibility criteria of phase III randomized controlled trials in heart failure (HF) define a target population in which an intervention is most likely efficacious.[1,2] However, restrictive eligibility criteria are a long-standing concern that can jeopardize trial accrual and lead to overly narrow trial populations.[3] In the latter, the generalizability of study results to real-world patients becomes compromised, causing uncertainties in treatment decisions for under-represented subgroups of women, older persons, and multi-comorbid patients. Potentially, is it the patient population with more complex diseases that would benefit the most from treatment.

HF trials have become larger and take longer to complete as a series of successful drug therapies have translated to an initial decline in mortality.[4] Although this decline in mortality has since plateaued,[5,6] proving the incremental benefit of new therapy amid existing background treatment becomes more challenging. In efforts to enrich for outcome events, inclusion and/or exclusion criteria can become more complex and restrictive and thus run the risk of low enrolment, protocol amendments, or non-completion.[7] Of the 644 HF trials on ClinicalTrials.gov from 2005 to 2015, more than half of study terminations were due to poor accrual.[8] Decisions on the inclusion and exclusion criteria of a trial clearly affect its length and cost.[3] It is thus time to move from carry-forward criteria selection to one that is data guided.[9] This approach decreases reliance on assumed recruitment rates, thereby minimizing opportunity costs lost from protocol amendments or study extensions.

Another key change in trials for HF is the rise in globalization for reasons such as growing trial sizes, lower research costs in developing nations, and market expansion.[10] With larger geographical differences also comes greater heterogeneity in patient characteristics and outcomes of these 'megatrials'.[4] In the EVEREST trial for hospitalized HF, regional differences were evident for patient comorbidities, biomarkers, treatment, and outcomes.[11] Disparities in patient characteristics directly impact enrolment at international sites. In this respect, characterization of regional variation, for instance, between Western Europeans and Asians with HF and understanding how these differences impact patient eligibility, enables early anticipation of differential accrual across international sites.

Estimating eligibility in real-world data (RWD) before study commencement facilitates optimization between internal validity, generalizability, and trial efficiency. In this study, we aim to compare the influence of the most commonly used eligibility criteria for trials in HF with reduced ejection fraction (HFrEF) on eligibility between two patient populations, a European and an Asian registry cohort. As a secondary objective, we assessed the theoretical impact of the gradual addition of common inclusion and exclusion criteria on overall trial patient eligibility.

Methods

Selection of heart failure trials

Clinical study registration as of 31 December 2021 was downloaded from Aggregate Analysis of ClinicalTrials.gov,[12] a daily updated trial registration database.[13] Relevant studies were identified by the 'condition or disease' of HF and its equivalent terms (Supporting Information, *Table S1*). We characterized all interventional studies for HF and then focused our analysis on the eligibility criteria for phase III trials for HFrEF, defined as trials that included patients with a left ventricular ejection fraction (LVEF) of an upper limit of 40% or below.

The primary variable analysed was the free text trial eligibility criteria. Other trial-related variables were analysed as potential predictors of patient eligibility. These were the study's start year, anticipated sample size, and intervention type. In addition, we defined the primary funder as the following: industry-funded if its lead or collaborator is industry; National Institutes of Health (NIH)/other government agency if present as lead or collaborator for a non-industry-sponsored study; and otherwise, it is a healthcare, academic institution, or other.

Trial inclusion and exclusion criteria

The eligibility criteria for trials were extracted into a structured format from the original free text in the trial registration data. Natural language processing methods were used, and further details are found in Supporting Information, *Methods S1*. To calculate patient eligibility for trials, binary criteria such as the presence of comorbidities can be applied as an inclusion or exclusion criterion, whereas continuous variables, that is, laboratory and physical examination measurements, are specified as numerical ranges. Arbitrary limits of 0 and a maximum of 2000 were used if upper and lower limits were not explicitly specified.[14] The structured dataset on trial inclusion and exclusion criteria is available upon request by contacting the study authors.

Data sources for target population

A target population or domain refers to patients to whom trial findings are applicable, whereas a trial population is a subgroup within the target population. Target population data were available from two registries: the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) and the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry.[15,16] The former consists of European HF

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patients, while the latter consists of patients from 10 Asian countries. Both HF registries included physician-diagnosed HF patients. Only patients with LVEF $<$ 40% were included.

Registry variables were screened. The following variables were available across registries and applied in the estimation of eligibility scores: age, anaemia, atrial fibrillation (AF), body mass index, cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), serum creatinine, device therapy, diastolic and systolic blood pressure, estimated glomerular filtration rate (eGFR) by the CKD-EPI equation, haemoglobin, heart rate, LVEF, history of myocardial infarction (MI), serum potassium, QRS duration, revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), stroke, sinus rhythm, use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin-II receptor blockers (ARBs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and history of worsening HF (HF hospitalization in the past 6 months for ASIAN-HF or 12 months for BIOSTAT-CHF). Because of substantial missing rates, natriuretic peptides were not analysed. Valve disease was not evaluated due to insufficient depth on severity, and most trials exclude only the severe forms.

Estimating eligibility in existing trials

We estimated overall and single-criterion eligibility based on the generalizability index for the study trait, GIST 2.0, introduced by Sen *et al*.[14,17] The score represents an estimated proportion of the target population that is trial eligible, with values between 0 and 1. This eligibility score is first calculated by treating each criterion independently, be it the presence or absence of characteristic(s) or the fulfilment of defined thresholds in numeric measurements. Then, an overall weighted representativeness score is estimated based on the proportion of registry patients who fulfil all criteria. Patient weights were estimated as a residual difference from a non-linear Gaussian kernel-based hypersurface plane. The estimation method standardizes numeric data and accounts for interdependence across criteria in each trial. To determine the criterion most likely to impact patient eligibility, eligibility scores were inversely weighted by the frequency of occurrence in trials, whereby the lowest weighted scores would reflect the most restrictive criteria.

Missing data in the registries ranged from 1% to 54% and were dealt with using multiple imputation by chained equations.[18] The number of imputations was set at 10.[19] Statistical analysis was performed using R statistical software 4.1.2 (R Core Team, 2021), STATA SE 15 (StataCorp LP, College Station, TX, USA), and MATLAB R2021a. Statistical significance was set at 0.05.

Eligibility in theoretical trials

Lastly, we sought to determine how eligibility changes with each addition of commonly used eligibility criteria. We started with a broad set of criteria including (i) age between 18 and 80 years; (ii) LVEF $\leq$ 40%; (iii) New York Heart Association (NYHA) classes II–IV; (iv) double background therapy of any dose of ACE-I/ARB + BB; (v) no MI/PCI/CABG; (vi) no device therapy; (vii) no cancer/COPD; (viii) no stroke; (ix) renal function (eGFR $>$ 30 mL/min/1.73 m^2); (x) haemoglobin $>$ 10 g/dL; and (xi) potassium $<$ 5.5 mmol/L. Alternative scenarios with more restrictive selection, including (i) an LVEF of 35%, (ii) only NYHA classes II and III, (iii) enrichment with previous hospitalization for HF, and (iv) triple therapy (including MRA), were also considered to determine the impact of stricter cut-offs on eligibility.

Results

Characteristics of heart failure phase III trials

As of December 2021, 4425 studies for HF were identified on ClinicalTrials.gov, and 375 were phase III HF trials. Of these, 163 (44%) were HFrEF trials, 9% were HF with preserved ejection fraction (HFpEF) trials, 30% were non-selective for LVEF, and a remaining 17% enrolled hospitalized HF patients (*Table 1*). Within a 37 year observation period, the number of phase III trials registered per decade was increasing, with more than half (55%) initiated within the recent decade. The size of trials was also increasing with time, specifically from 2005 onwards ($P < 0.001$). By subtype, the largest trial size was in HFpEF trials (median 336) vs. the overall median HF trial size of 170 patients. Drugs were the most common intervention (68%), and half of the trials (51%) were industry-funded.

Inclusion and exclusion criteria in heart failure with reduced ejection fraction trials

Figure 1 displays the most frequently used eligibility criteria. HFrEF trials predominantly selected participants by NYHA class (69%), while almost a quarter included patients based on previous worsening or hospitalization for HF (23%), and natriuretic peptide level (18%). A range of patient medical histories or comorbidities were generally applied as exclusion criteria, and the most common were acute coronary syndrome (64%), valvular heart disease (47%), pregnancy or lactation (44%), previous or planned implantation of cardiac devices (44%), coronary revascularization (37%), and stroke (33%). Measures of organ dysfunction and performance status most often used were renal function (55%), hepatic

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Table 1 Heart failure phase III trial characteristics

	Outpatient									
	HFrEF		HFpEF		Any EF		Hospitalized HF		Total	
N (%)	163	43.5%	33	8.8%	114	30.4%	65	17.3%	375	100%
Start year										
1985–2005	42	25.8%	2	6.1%	23	20.2%	13	20.0%	80	21.3%
2006–2010	36	22.1%	7	21.2%	31	27.2%	16	24.6%	90	24.0%
2011–2015	48	29.4%	5	15.2%	27	23.7%	16	24.6%	96	25.6%
2016–2022	37	22.7%	19	57.6%	33	28.9%	20	30.8%	109	29.1%
Trial size										
Median (IQR)	160	50, 402	336	52, 1490	130	51, 330	255	112, 654	170	54, 505
0–50	41	26.1%	8	24.2%	28	24.8%	11	16.9%	88	23.9%
51–100	26	16.6%	6	18.2%	21	18.6%	3	4.6%	56	15.2%
101–200	19	12.1%	0	0.0%	23	20.4%	13	20.0%	55	14.9%
201–500	36	22.9%	4	12.1%	18	15.9%	18	27.7%	76	20.7%
500+	35	22.3%	15	45.5%	23	20.4%	20	30.8%	93	25.3%
Missing	6		0		1		0		7	
Intervention type										
Drug	107	65.6%	32	97.0%	60	52.6%	60	92.3%	240	68.2%
Device	33	20.2%	0	0%	27	23.7%	3	4.6%	60	17.0%
Behavioural	11	6.7%	0	0%	17	14.9%	2	0%	29	8.2%
Procedure/diagnostic	13	8.0%	1	3.0%	6	5.3%	1	3.1%	25	7.1%
Biological	7	4.3%	0	0%	6	5.3%	0	0%	11	3.1%
Dietary	2	1.2%	0	0%	4	3.5%	1	1.5%	5	1.4%
Primary sponsor										
Industry	78	47.9%	19	57.6%	55	48.2%	38	58.5%	190	50.7%
Academic/healthcare institution	53	32.5%	10	30.3%	39	34.2%	20	20.8%	122	32.5%
NIH/other gov agency	26	16.0%	3	9.1%	15	13.2%	7	10.8%	51	13.6%
Others[a]	6	3.7%	1	3.0%	5	4.4%	0	0%	12	3.2%

EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; NIH, National Institutes of Health.
HFpEF trials were those that recruited only patients with left ventricular ejection fraction ≥ 40%; hospitalized HF trials evaluated therapies in acute decompensation or hospitalized patients; and the remaining are categorized as non-left ventricular ejection fraction selective trials.
[a]Others include managed care or non-profit organizations, individual investigators, and networks.

function (21%), and anaemia (anaemia status or haemoglobin cut-off) (17%).

Also gaining importance are concomitant background treatments. Half (48%) required participants to be on standard of care medical and/or device therapies, in which a quarter specified ACE-I/ARB (28%) or BB (25%) background therapy, and a smaller percentage required participants to be on MRA (11%). Current use of intravenous therapy, including diuretics, inotropes, and vasopressors, was specified in 2% of HFrEF trials, largely as an exclusion criterion.

Eligibility for trial enrolment by Asian and European populations

To determine the proportion of patients who were trial eligible, 2545 and 4868 patients from the BIOSTAT-CHF and ASIAN-HF registries were included for analysis (*Figure 2*). Baseline characteristics are presented in Supporting Information, *Table S2*. Compared with the Asian registry, European patients were older (median age 70 vs. 61 years), more frequently in NYHA classes III or IV (38% vs. 30%), and had a lower prevalence of prior HF hospitalization (30% in 12 months vs. 39% in 6 months). The rate of comorbidities was generally higher in European patients, most notably ischaemic heart disease (68% vs. 52%), AF (43% vs. 18%), and COPD (17% vs 8%), except for chronic renal disease (31% vs. 47%). The use of HF medications between populations was similar for ACE-I/ARB, BB, and MRA. Almost all European registry patients were on diuretics (99.5% vs. 82%), as this was a requirement for participation in BIOSTAT-CHF.

Between 1 and 14 eligibility criteria were applied in the estimation of eligibility. Summarizing across 163 HFrEF trials, about one-fifth of the combined target population were eligible [median eligibility score: 0.19 (95% confidence interval: 0.14, 0.24)]. *Figure 2* shows that the distribution of eligibility scores across trials was broadly similar between Asian and European populations. Median eligibility was marginally higher in Asian patients (0.20 vs. 0.17) but was not statistically significant ($P = 0.18$).

Table 2 displays median eligibility scores by trial characteristics. Eligibility for trials declined with time by more than half, from 0.40 to 0.14, between trials initiated in 1985–2005 and 2006–2015. Interestingly, trials from the recent 7 years show a reversal, increasing to a median eligibility of 0.19 ($P = 0.03$). By intervention type, drug trials had a larger representation of the target population (median score 0.25) compared with device and procedural or diagnostic trials

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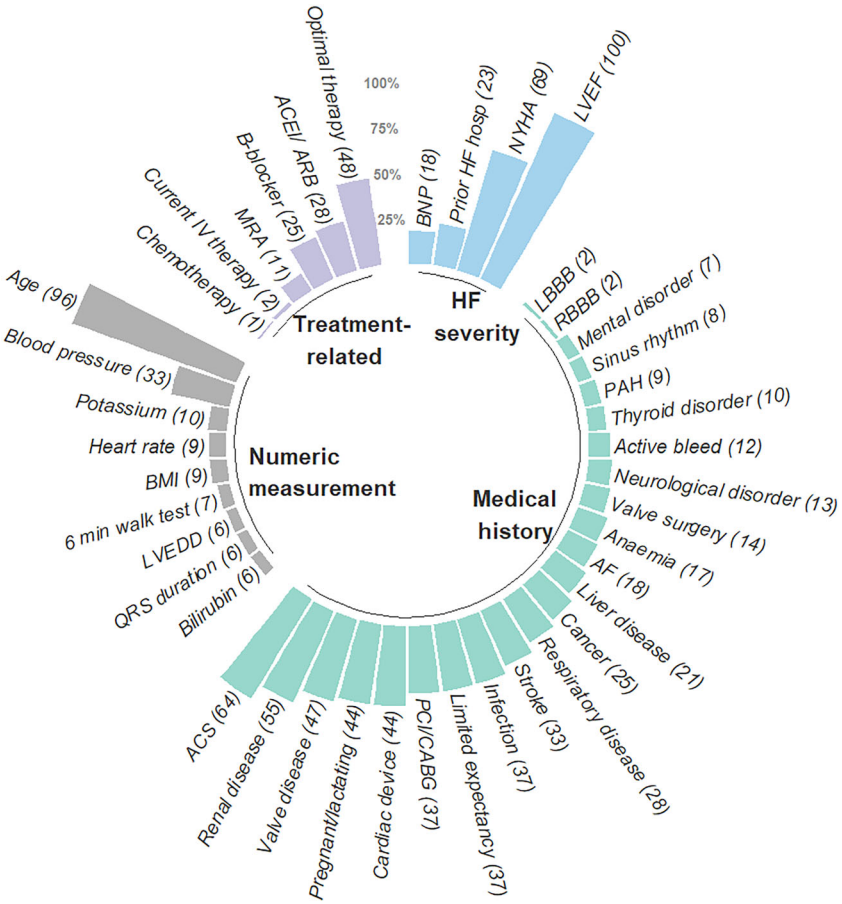
Figure 1 Ranked eligibility criteria in heart failure (HF) with reduced ejection fraction trials (n = 163). Values in brackets indicate percentages. Anaemia includes iron deficiency/anaemia and haemoglobin and ferritin thresholds. Renal disease includes serum creatinine, estimated glomerular filtration rate, and chronic or end-stage renal disease. Optimal therapy refers to required background therapy, whether medication or devices are considered standard of care at the time of study. ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin-II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; IV, intravenous; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAH, pulmonary artery hypertension; PCI, percutaneous coronary intervention; RBBB, right bundle branch block.



(median scores were both 0.09, $P < 0.001$). Further, patient eligibility differed by primary funding source; eligibility was highest among academic/healthcare institution-funded trials, followed by NIH-funded trials, and lastly, industry-sponsored trials. The anticipated size of trials, however, was not predictive of eligibility (P = 0.5).

Comparing impact of individual criterion by target population

Patient eligibility can be limited when one or more exceptionally restrictive criteria are present. Of the criteria assessed, prior HF hospitalization, MRA background treatment, and anaemia were the most restrictive, with eligibility scores of 0.38, 0.56, and 0.61, respectively (*Figure 3*). Eligibility based on a single criterion was comparable between Asian and European patient populations, with a few exceptions. Prior HF hospitalization, history of MI, normal sinus rhythm, and cardiac devices were more restrictive among European patients, resulting in 26%, 20%, 20%, and 13% lower eligibility compared with Asian patients. On the other hand, for trials that focused on devices or iron supplementation, QRS duration and anaemia status or serum haemoglobin were comparatively more restrictive in Asian patients, with relative differences of 33% and 14% lower eligibility. Upon inverse-frequency weighting of each criterion, the most restrictive were prior MI, NYHA functional class, age, and prior HF hospitalization (Supporting Information, *Figure S1*).

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Figure 2 Distribution of the proportion of patients eligible for phase III trials by registry population and eligibility criteria ranked by restrictiveness in patient selection. ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

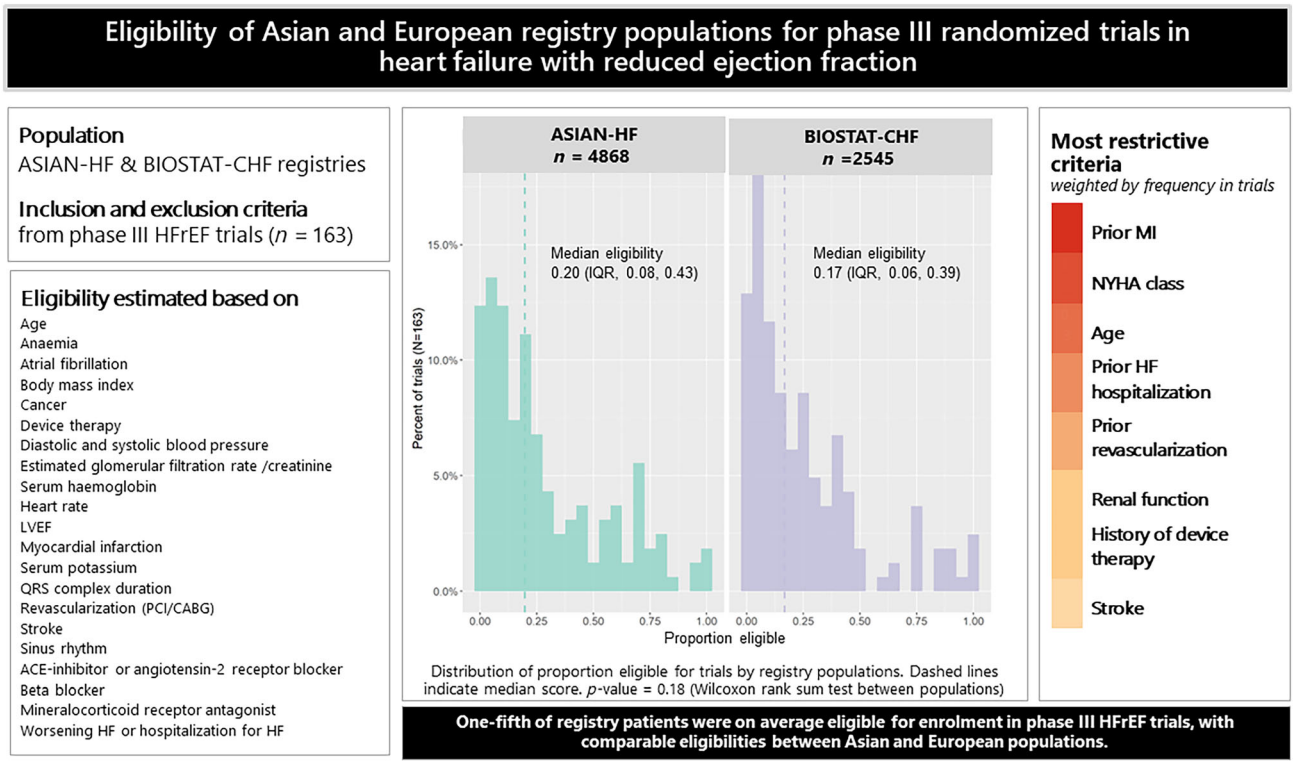

Table 2 Median eligibility by heart failure with reduced ejection fraction trial characteristic

	n	Median score	*P*-value[a]
Start year			**0.03**
1985–2005	42	0.40	
2006–2010	36	0.15	
2011–2015	48	0.14	
2016–2022	37	0.19	
Intervention type			**<0.001**
Drug	102	0.25	
Device	33	0.09	
Procedural/diagnostic	10	0.09	
Behavioural/dietary	13	0.40	
Biological	5	0.05	
Primary funder			**0.01**
Industry	78	0.13	
Academic/healthcare institution	53	0.27	
NIH/government agency	26	0.23	
Others[b]	6	0.19	
Trial size			
≤50	41	0.23	0.5
51–150	36	0.13	
151–400	40	0.16	
401–8500	40	0.19	
Missing	6		

NIH, National Institutes of Health.
Bold *P*-values indicate statistical significance.
[a]Kruskal–Wallis rank sum test.
[b]Others include managed care or non-profit organizations, individual investigators, and networks.

Eligibility using multiple criteria in a theoretical trial design

For a theoretical design, the strongest determinants of eligibility were background therapy of ACE-I/ARB and BB and history of MI or coronary revascularization by PCI or CABG, in which half and a third of patients remain eligible, respectively, when these are considered in addition to liberal ranges for age, LVEF ≤ 40%, and NYHA functional classes II–IV (*Figure 4A*). Factoring a further exclusion of patients with implanted devices, COPD, cancer, stroke, eGFR ≤ 30 mL/min/1.73 m^2, haemoglobin < 10 g/dL, and potassium ≥ 5.5 mmol/L leaves about one-fifth (18%) eligible. Eliminating NYHA class IV led to only a marginal decrease in total eligible participants (17%) (*Figure 4B*). Similarly, a stricter upper limit for LVEF at ≤35% resulted in eligibility that is not different from LVEF ≤ 40% (*Figure 4C,D*), indicating that eligibility was more strongly driven by background HF therapy than LVEF or NYHA functional class.

In an alternative design with prior HF hospitalization as cardiovascular risk enrichment, overall eligibility became substantially restricted from 18% to 5% remaining eligible (Supporting Information, *Figure S2*). For a trial design that considers a triple HF background therapy (add-on MRA),

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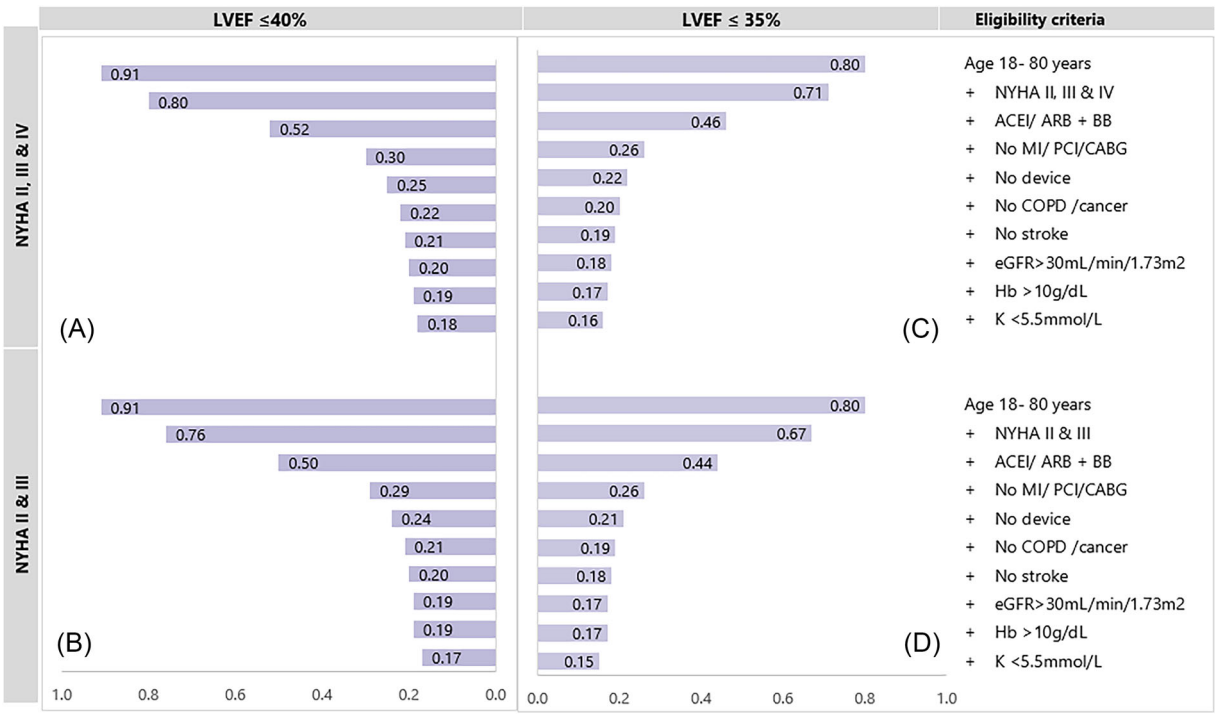
Figure 3 Ranked unweighted eligibility scores per criterion by target populations (from most to least restrictive). Values in brackets represent the percentage of heart failure (HF) with reduced ejection fraction trials (*n* = 163). ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-II receptor blocker; BB, beta-blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention. [a]Typically, exclusion criterion.

Population	QRS duration (6%)	Prior HF hospitalization (23%)	MRA (11%)	Anemia (15%)	Sinus rhythm (8%)	MI[a] (55%)	PCI/ CABG[a] (37%)	AF[a] (18%)	ACEI / ARB (28%)	BB (24%)	Device[a] (33%)
All	0.38	0.38	0.56	0.61	0.64	0.64	0.69	0.72	0.77	0.81	0.81
Asian	0.33	0.42	0.58	0.58	0.70	0.70	0.71	0.82	0.78	0.79	0.86
European	0.44	0.31	0.52	0.66	0.56	0.56	0.67	0.57	0.75	0.83	0.75

Population	NYHA (69%)	COPD[a] (11%)	eGFR[a] / creatinine (55%)	Stroke[a] (33%)	Systolic + diastolic BP (29%)	Potassium (10%)	Cancer[a] (25%)	BMI (9%)	HR (9%)	Age (76%)	LVEF (100%)
All	0.84	0.88	0.90	0.91	0.93	0.96	0.97	0.97	0.98	0.99	1
Asian	0.82	0.92	0.90	0.93	0.93	0.96	0.97	0.97	0.99	0.99	1
European	0.87	0.83	0.91	0.89	0.93	0.96	0.96	0.97	0.98	0.99	1

Most restrictive — Least restrictive

Figure 4 Cumulative eligibility for theoretical heart failure trials per addition of eligibility criteria stratified by (A) left ventricular ejection fraction (LVEF) < 40% and New York Heart Association (NYHA) II–IV; (B) LVEF < 40% and NYHA II and III; (C) LVEF ≤ 35% and NYHA II–IV; and (D) LVEF ≤ 35% and NYHA II and III. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, beta-blocker; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; MI, myocardial infarction; PCI, percutaneous coronary intervention.



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overall eligibility was halved in comparison with a broader double therapy of ACE-I/ARB + BB (Supporting Information, *Figure S3*).

Discussion

In this study, we characterized all registered phase III HF trials by their subtype and eligibility criteria, specifically for HFrEF. There are four key findings. First, the patient characteristics most frequently used for selection in HFrEF trials were indicators of HF severity, namely, LVEF, NYHA class, prior worsening of HF, natriuretic peptides, followed by cardiovascular comorbidities and events/procedures, that is, history of MI, cardiac devices, revascularization, and optimized background HF treatment. Second, the eligibility of two distinct HF patient populations for existing HFrEF trials did not significantly differ; they were both low in that only 20% of patients, on average, were eligible. Third, accordingly, we identified the most restrictive individual criteria, and these were prior HF hospitalization, MRA background treatment, and anaemia. When frequency in trials is taken into consideration, prior MI, NYHA functional class, age, and prior HF hospitalization had the highest impact on restrictiveness. Fourth, as eligibility criteria work collectively rather than independently in patient selection, we have evaluated available RWD against eligibilities for trials and showed that we can test assumptions on the impact of combinations of eligibility criteria on trial accrual.

It is reassuring to note that patients from the Asian registry population have equal, if not slightly higher, eligibility for phase III HFrEF trials compared with European patients, although most clinical trials are designed and weighted towards Western Europe and North American populations.[20,21] This is especially important as clinical trials increasingly gear towards cross-continent sites, including those in Asia, for both scientific and ethical reasons. Although large pharmaceutical markets in Asia, such as China and Japan, no longer require local data for market authorization, foreign clinical trial data will nevertheless be scrutinized for ethnic and other inconsistencies, and if present, add-on local bridging studies will incur costs.[22] On this note, incorporating global sites, for instance, in Asia at the planning stage, is cost-efficient given its high disease burden.[22]

On overall eligibility, having only one-fifth of the target population that is eligible reveals a sizeable gap in representation of real-world patients. This average is comparable with eligibility estimates of single contemporary HFrEF drug trials, which ranged between 11% and 35%.[23–25] Although estimates found for HFrEF trials are higher than the other large-scale eligibility criteria analyses of cancer (2–5%) and diabetes trials (5%), there remains much room for improvement.[3,14] Variation in eligibility between trials could be explained in part by the trial intervention type. Those that evaluated drugs make up the majority of explanatory trials in HFrEF and are, as expected, more representative than device or procedure trials with a 25% average eligibility. Trials for cardiac devices and procedures are more restrictive as these target small subsets of patients with arrhythmia or conduction problems, advanced HF, or require device optimization. Next, it is important to recognize that eligibility for HFrEF trials has been declining since the early 2000s, with a slight increase in more recent years as a consequence of improved trial registration with time[26] and growing lists of eligibility criteria, including those for prognostic enrichment.[7] The availability of numerous guideline-directed drug therapies [guideline-directed medical therapies (GDMTs)] has to an extent decreased mortality in HFrEF, making present-day HF trials increasingly difficult, complex, and costly to conduct.[11,27]

While maintaining as broad a population as possible, excluding patients at either end of the disease severity spectrum (LVEF 36–40%) or NYHA class IV did not influence the overall proportion of eligible patients. Conversely, adding a history of HF hospitalization substantially reduced the proportion of eligible participants, suggesting that use of this criterion should be approached with care, particularly for HFrEF, although it is deemed useful to drive event rates in HFpEF trials.[25,28] Rather than restricting a trial sample to only patients who meet cardiovascular enrichment criteria, newer adaptive trial designs have been proposed to allow for data from both target and non-target subpopulations, particularly if the sensitivity of a prognostic marker is not fully understood.[29,30]

Although the exclusion of patients with recent cardiovascular instability can be explained from a safety perspective, it is harder to justify the comorbidity-based exclusion of patients with iron deficiency/anaemia, COPD, chronic renal disease, and cancer, which are present in up to more than half of people with HF.[31–33] Rather than solely presenting with competing risks, co-existing chronic renal disease and iron deficiency/anaemia contribute independently to subsequent cardiovascular events.[34,35] Therefore, phase III HF trials should generally be inclusive of these comorbidities unless explicitly justified by unacceptable safety risks such as advanced disease, contraindication, involvement with drug metabolism or excretion, or interference with primary endpoint assessment.

Considering difficulties in defining a single optimal GDMT, the Heart Failure Collaboratory agrees that a gradient of options, from (i) no background therapy to (ii) any dose of ACE-I/ARB/angiotensin receptor-neprilysin inhibitor plus BB therapy, and then (iii) adding an MRA to finally meet the strictest requirement of (iv) 100% target doses of all GDMT with sodium-glucose cotransporter-2 inhibitors, could be considered.[36] In the present study, we assessed the impact of including any dose background therapy of ACE-I/ARB and BB and found between 10% and 30% absolute decrease in eligibility, which seems like a fair trade-off, particularly for eval-

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uating the incremental benefit of add-on therapies. However, stepping up required background therapy to include MRA substantially lowers eligibility by two-thirds, highlighting the need to base decisions for selection criteria not only on guideline recommendations but also on the actual use of these GDMTs. Instead of mandating specific drug classes, this alternative enables a common score to summarize the type and intensity of background treatment as the basis for comparison within and between trials.[36]

Among the strengths of this study is the extensive analysis of eligibility criteria for trials on ClinicalTrials.gov, which is among the most complete trial registers on drugs and devices by major pharmaceutical companies.[13] As therapeutics are eventually aimed at global markets, assessing eligibility using multinational registries from Asia and Europe enables testing the hypothesis of equal eligibility across patient profiles. There are also several limitations to this study. Information on the trial phase was not available for 54% of studies labelled as interventional. Natriuretic peptide levels as a criterion could not be compared here due to incomplete data from the ASIAN-HF registry. That said, this diagnostic and prognostic criterion is infrequently measured in limited resource settings, and selecting natriuretic peptides is known to affect the distribution of trial patient characteristics,[2] raising further questions on generalizability. Also, current registry data do not provide sufficient granularity to assess the use of intravenous diuretics as a 'stabilization' criterion for patient eligibility. Next, the eligibility criteria recorded on ClinicalTrials.gov represent only part of the full list. Thus, the proportion of eligibility criteria here is likely underestimated. Similarly, because only a subset of criteria could be accounted for when calculating eligibility scores, these would be overestimated compared with actual eligibility. As the definitions for HF subtypes by LVEF evolve with time, the HF with mildly reduced ejection fraction subtype is more likely covered within the HFrEF trials, with some minimal overlap with the HFpEF trials.

It is necessary to acknowledge that both ASIAN-HF and BIOSTAT-CHF cohorts each apply selection criteria and therefore have a narrower spectrum of real-world patients than those within electronic medical records (EMRs). Nonetheless, present challenges such as an inherent lack of clarity in analogue clinical text, unstructured data formats, and restrictions on single centres or payers[37] preclude the use of EMRs for large-scale comparisons. For these reasons, HF registries represent the next best data source, given that they are specifically designed for the disease and have the benefits of rigorous data quality controls, completeness, and multinational patients. Lastly, temporal characteristics for event- or procedure-based criteria such as time from revascularization could not be determined in the patient data and, as they were commonly a basis for exclusion, could result in an underestimation of eligibility.

In the present study, we have shown the merits of characterizing eligibility in two distinct target populations. For instance, the exclusion of patients with AF or a history of MI will lead to comparatively slower accrual in European sites. Conversely, cardiovascular enrichment with previous HF hospitalization potentially leads to quicker enrolment rates in the Asian population, given that the proportion with prior hospitalization is already a third higher than the European cohort in its shorter observation period of 6 months. Second, we demonstrate the feasibility of simulating combinations of eligibility criteria using cohort data before designing a new trial. This step can easily be added at pre-design stages to confirm assumptions and anticipate potential challenges to recruitment.[9] To improve the generalizability of future HF trials, patient exclusion based on non-cardiovascular comorbidities such as renal disease, anaemia, and chronic pulmonary conditions should be adequately justified. Lastly, instead of obligatory quadruple background HFrEF treatment, trial designers can opt for less strict criteria on background treatment and subsequently characterize them as subgroups by dose and therapeutic class using a GDMT score.[36] A future research direction is to model the impact of each eligibility criteria scenario on the accrual of endpoints or hazard ratios. Existing challenges related to unstructured data formats, data sharing restrictions, and data quality of electronic health records can be overcome to simulate trial inclusion in real time and incorporate new disease markers or treatments as disease knowledge advances.

Conclusions

Based on an analysis of 163 trials over 37 years, we show that one-fifth of registry patients were, on average, eligible for enrolment in phase III HFrEF trials, with comparable eligibilities between Asian and European populations. On a broad perspective for HFrEF therapeutics, criteria that had the largest impact on both patient selectivity and frequency in trials were prior MI, NYHA class, age, and previous HF hospitalization.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Heart failure and equivalent terms.
Table S2. Patient characteristics for BIOSTAT-CHF and ASIAN-HF registries.
Figure S1. Trial criteria organised by proportion of eligible patients and frequency of the criterion in HFrEF trials. Values below criteria indicated eligibility scores inversely weighted by proportions of trials for each criterion, smaller values indicate larger impact on representativeness.
Figure S2. Cumulative eligibility for theoretical heart failure trials per addition of eligibility criteria with an enrichment criterion of prior HF hospitalization.
Figure S3. Cumulative eligibility for theoretical heart failure trials per addition of eligibility criteria comparing between double (any dose ACEI/ARB + BB) and triple therapy (any dose ACEI/ARB + BB + MRA).

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