Generalizability of Randomized Controlled Trials in Heart Failure
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Author: Yvonne Mei Fong Lim
Cover design: Amin Adli Bin Dolbaharin and John Paul Snead
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Generalizability of Randomized Controlled Trials in Heart Failure

Generaliseerbaarheid van gerandomiseerde klinische trials in hartfalen

(met een samenvatting in het Nederlands)

Hasil percubaan klinikal dan aplikasi secara umum bagi pesakit kegagalan jantung

(dengan ringkasan dalam Bahasa Melayu)

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Mei Fong Lim

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te Selangor, Maleisië

Promotoren:
Prof. dr. F.W. Asselbergs
Prof. dr. D.E. Grobbee

Copromotoren:
Dr. C.H. Vaartjes
Dr. S. Koudstaal

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General Introduction

INTRODUCTION

Clinical practice guidelines are developed for the general heart failure population and their evidence generally depend on randomized controlled trials. However, clinical trials are often criticized for poor generalizability, and this is among the cited reasons for underuse of effective treatments. For instance, lack of trial data in older patients explains in part the under-prescribing of warfarin in patients aged 75 years and above; the group who has the highest prevalence for non-rheumatic atrial fibrillation and also at highest risk without treatment.[1–3] Historically, younger, white men were considered the normative population in heart failure trials whereas women or older persons were expected to have similar responses.[4–6] However, recent post-hoc analyses of cardiac resynchronization therapy (CRT) trials revealed that females were more likely to respond to CRTs and at shorter QRS complex duration than men[7,8] whereas observational studies demonstrate that women benefited from lower doses than guideline recommended target doses of beta-blockers and RAAS-inhibitors,[9] suggesting that this one-size-fits-all approach is flawed.

Extrapolation of clinical trial results to its population of interest is often broadly described as external validity. It reflects a complex assessment of patient selection, trial setting, differences between trial and routine practice, outcome measurement and statistical methods.[1,10] In this context, terms including generalizability, applicability, transferability, transportability and extrapolation have been used with overlapping meanings.[1,10,11] The present thesis focuses on generalizability, defined as making inference from a study sample back to the target population, e.g. the domain (inclusive of the study population).[11]

While it is neither realistic nor reasonable to expect generalizability to every patient and setting, it can be assessed and described to allow clinicians, regulators and policy makers decide to whom trial results are applicable.[1] Moreover, standardizing assessments of generalizability in current trials will pave the way for improving future trials. One way to formally ensure generalizability is by replicating the study in its new target population as effectiveness or pragmatic trials but this is impractical and very expensive to implement widely.[10,12] In the absence of guidelines on trial generalizability assessment, another approach would be to conduct secondary data analyses in heart failure trial datasets, trial registers and observational cohort data.[1,12] These methods can be classified into those involving emulation of

existing or hypothetical trials and after-the-fact analysis of trial data sets[13] and both approaches will be covered in this thesis.

Inadequate generalizability can arise from under-representation of important subgroups among people with heart failure such as those of older ages, women, minority ethnic groups. Questions arise to whether meaningful differences exist for outcomes within these subgroups as patient characteristics are increasingly shown to be modifiers of treatment effect or safety. Racial differences in incidence and outcomes are well-established in studies in the U.S., in which Black and Hispanic/Latinx persons with heart failure are known to fare worse than White patients.[4] This is attributable to a disproportionate burden of CV risk factors that leads to earlier onset of atherosclerotic disease and shorter life expectancy. Risk differences between racial groups are linked to social and system/institutional determinants of health, which cannot be ignored when considering the effectiveness of treatments in real-world heart failure patients. With that said, a broad racial category such as Asians can be heterogenous in terms of culture, ethnic, language and biology. For instance, people of South Asian and East Asian origins have marked differences in the prevalence of ischemic heart disease and its subsequent disease outcomes.[4] For heart failure, inter-ethnic differences in prognosis among diverse South East Asian communities is much less understood compared to those on racial disparities in the U.S.

On a similar note, people with multimorbid conditions are often excluded from heart failure trials. And yet it is likely that they are part of the population treated with an approved drug, despite a disproportionately small amount of data on safety. Given that extensive exclusion criteria limits target population representativeness and trial accrual rates (57% of terminated trials were terminated because of poor accrual[14]), knowing how individual criteria affects eligibility in a collective manner would be of added value at the design stage of trials.

Among the challenges to assessing generalizability in trials for heart failure, is that it requires access to trial datasets but this is limited particularly for pharmaceutical industry-sponsored trials. Public-private partnerships such as the BigData@Heart project[15,16], has enabled sharing of individual patient data for direct comparison of trial populations and heart failure registries. From here, we examine generalizability in terms of heart failure outcomes among enrolled trial participants relative to observational registry patients, quantify age, sex and ethnic differences in

heart failure incidence and outcomes and assess the impact of eligibility criteria on the representativeness of heart failure trials.

Aims of thesis

The main aim of this thesis is to investigate generalizability of clinical trials for heart failure with reduced ejection fraction (HFrEF). The objectives of this thesis take three perspectives. First, we contrast patient characteristics and estimate generalizability of heart failure trials to observational registry cohorts. Because clear differences exist between trial and registry populations, we will include case-mix-adjusted outcome comparisons between study populations. In addition, we compare generalizability of these trials by outcomes in men and women. For the second objective, we assess at the design stage of trials, the impact of eligibility criteria of randomized trials on patient representativeness within European and Asian heart failure registries and subsequently in hypothetical trials by stepwise addition of the most commonly used criteria. Lastly, we focus on disentangling differences in incidence and heart failure outcomes by sex and ethnicity in a multi-ethnic community to highlight the importance of patient subgroup representation and diversity in future trials.

OUTLINE OF THIS THESIS

In the first part of this thesis (Chapter 2.1), we explore the differences between trial participants and registry cohorts and examined how risk factor adjustments affected the standardised mortality ratios between the populations. In Chapter 2.2 we identified the most frequently used inclusion and exclusion criteria for phase III HFrEF trials registered in ClinicalTrials.gov and subsequently compared eligibilities for the trials, based patient characteristics from an Asian and European registry cohort. In chapter three, we focus on demographic representation of trial populations. First, we determine whether all-cause and cardiovascular mortality outcomes for males and females in HFrEF trials differed from their counterparts in the registry cohort. In chapter 3.1 Next in chapter 3.2, we investigate the incidence of heart failure hospitalization and its 10- year trends by age, sex and ethnicity in a multiracial population in Malaysia. In chapter 3.3, we determine trends in prognosis of heart failure, in terms of readmission and mortality, differentiating between age, sex and ethnicity.

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2

Comparing heart failure trial and registry populations

Chapter 2.1

Generalizability of Randomized Controlled Trials in Heart Failure with Reduced Ejection Fraction

Yvonne Mei Fong Lim
Megan Molnar
Ilonca Vaartjes
Gianluigi Savarese
Marinus JC Eijkemans
Alicia Uijl
Eleni Vradi
Kiliana Suzart-Woischnik
Jasper J. Brugts
Hans-Peter Brunner-La Rocca
Vanessa Blanc-Guillemaud
Fabrice Couvelard
Claire Baudier
Tomasz Dyszynski
Sandra Waechter
Lars H Lund
Arno W Hoes
Benoit Tyl
Folkert W Asselbergs
Christoph Gerlinger
Diederick E Grobbee
Maureen Cronin
Stefan Koudstaal

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ABSTRACT

Background

Heart failure (HF) trials have stringent in- and ex- clusion criteria, but limited data exists regarding generalizability of trials. We compared patient characteristics and outcomes between patients with HF and reduced ejection fraction (HFrEF) in trials and observational registries.

Methods and Results

Individual patient data for 16922 patients from five randomized clinical trials and 46914 patients from two HF registries were included. The registry patients were categorised into trial-eligible and non-eligible groups using the most commonly used in- and ex-clusion criteria. A total of 26104 (56%) registry patients fulfilled the eligibility criteria. Unadjusted all-cause mortality rates at one year were lowest in the trial population (7%), followed by trial-eligible patients (12%) and trial-non-eligible registry patients (26%). After adjustment for age and sex, all-cause mortality rates were similar between trial participants and trial-eligible registry patients (standardised mortality ratio (SMR) 0.97; 95% confidence interval (CI) 0.92 -1.03) but cardiovascular mortality was higher in trial participants (SMR 1.19; 1.12 -1.27). After full case-mix adjustment, the SMR for cardiovascular mortality remained higher in the trials at 1.28 (1.20- 1.37) compared to RCT-eligible registry patients.

Conclusion

In contemporary HF registries, over half of HFrEF patients would have been eligible for trial enrolment. Crude clinical event rates were lower in the trials, but, after adjustment for case-mix, trial participants had similar rates of survival as registries. Despite this, they had about 30% higher cardiovascular mortality rates. Age and sex were the main drivers of differences in clinical outcomes between HF trials and observational HF registries.

INTRODUCTION

Randomized controlled trials (RCTs) are the gold standard for evaluating the efficacy and safety of investigational therapies due to their robust methodology conducted within a strict regulatory framework.[1] A well-conducted RCT has high internal validity, which ensures that the observed treatment effect is directly the result of the therapy tested.[1–4] However, high internal validity can come at the expense of external validity, defined as the degree to which the treatment effect found in the study can be generalized and replicated outside the RCT.[1] If the RCT results found in the study population are not generalizable to the target population, it is unclear which patients in routine care can receive a treatment safely and effectively.[1–5]

Physicians' uncertainty and criticism of RCTs' generalizability has been suggested as one reason for the underuse of evidence-based treatments, specifically in the field of heart failure (HF).[2,6] There is currently no consensus on how to assess generalizability, but a logical and important first step is to assess if an RCT study population is representative of the projected target population.[2–4,7] Studies comparing summary data on baseline characteristics between RCTs and observational data have already been conducted, specifically for heart failure with reduced ejection fraction (HFrEF).[5,8–10] Although these studies have shown differences in crude outcomes between trial and real-world patients, it is not known how differences in patient characteristics drive the observed differences in prognosis. In addition, some of these comparisons have been limited by the small sample sizes from single trials.

Here, we compared individual patient data of five HFrEF randomized clinical trials and two HF registries by direct data access and collaboration between academic researchers and pharmaceutical industry partners. We first determined their differences in patient characteristics, treatment, and clinical outcomes. Then, we identified the proportion of registry patients who were eligible for inclusion in the trials and compared their outcomes with trial participants while adjusting for known prognostic factors of HF at the individual patient level.

METHODS

Data sources

Based on a collaboration with industry partners through the BigData@Heart Consortium[11], data access to patient level information was obtained for five randomized clinical trials in HFrEF patients.. BEAUTIFUL and SHIFT were ivabradine trials (n= 15732)[12,13], FAIR-HF and CONFIRM were studies on intravenous iron supplementation (n=763)[14,15] and PANTHEON was a trial for neladenosone bialanate (n=427).[16] Of these, three were phase III trials, one was phase II and lastly, one phase IV study. All RCTs included HFrEF patients based on left ventricular ejection fraction (LVEF) values (ranging from ≤ 35 to ≤ 45%) except for the BEAUTIFUL study, which recruited coronary artery disease (CAD) patients who had left ventricular dysfunction. To maintain comparability between patients from the RCTs, only patients with New York Heart Association (NYHA) class II-IV from BEAUTIFUL (n=9227) were included.

Aggregated data from both treatment and placebo arms of each RCT were pooled and compared against the HFrEF population from two observational data sources: the CHECK-HF and the SwedeHF registries.[17,18] Detailed information on the methods for both registries can be found elsewhere.[17,18] Briefly, the CHECK-HF registry included patients with chronic HF if they had an HF diagnosis based on ESC 2012 guidelines between 2013 and 2016.[17] The ongoing SwedeHF registry enrolled patients with clinician-judged HF patients in Sweden.[18] For the current analysis, outpatients registered between 2000 to 2016 (n=40 230) were included to ensure consistency with CHECK-HF.

Data from both registries were combined for describing patient characteristics and treatment but only SwedeHF data was used in the reporting on clinical outcomes because CHECK-HF did not have follow-up data. For each of the five trials, ethics approval and written informed consent were obtained by the respective study investigators.[12–16] CHECK-HF registry was granted ethics approval for anonymised analysis of existing patient data, while in the SwedeHF registry, enrolment was based on specific health centres' participation and patients allowed to opt-out should they wish not to participate.[17,18]

Eligibility criteria and outcomes

The inclusion and exclusion criteria listed in the study protocol of the five RCTs were tabulated (Supplementary Table 1) to identify common study entry criteria. These criteria were cross-checked for data availability within the registries and a set of most commonly used eligibility criteria was then identified to select subsets of RCT-eligible and non-eligible patients from the registries. The following inclusion criteria were used: age ≥18 years, LVEF<40%, NYHA functional class II to IV, on optimally-tolerated chronic HF medications of β-blocker and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blocker (ARB). Then, the following exclusion criteria were applied: serum haemoglobin concentrations <11g/dL in men or <10g/dL in women, chronic liver disease, creatinine >220μmol/L and cancer.

Comparisons were made based on (i) patient baseline characteristics (ii) cardiovascular medications and (iii) mortality outcomes. For summary statistics, aggregated data were extracted from each trial and there were instances of low patient numbers in the data contingency tables. To maintain patient anonymity, all table cells with counts of 3 and below were replaced with a central number of 2.[19] For HF medications, the percentage of patients who received <50% or ≥ 50% target doses of the HF medications were assessed (Supplementary table 2). Lastly, the following clinical outcomes at one year were assessed: all-cause mortality, cardiovascular mortality (ICD-10 codes I00 – I99) and first HF hospitalization (main diagnosis with codes I50, I11.0, I42.0, I42.3-I42.9, I43, I25.5, K76.1, I13.0, I32.2 or J81). Follow-up duration differed between the five trials. Three trials (BEAUTIFUL, CONFIRM-HF and SHIFT) had follow-up data for at least one year, so outcome at one year was reported here. The remaining two trials (FAIR-HF and PANTHEON) had less than a year's follow-up and patients were censored at the end of study.

Statistical analysis

Continuous data are presented as mean with standard deviation while categorical variables are reported in frequencies and percentages. Mean and proportion differences between the RCT and RCT-eligible registry patients were calculated and reported with their corresponding 99% confidence intervals (CI). Data are presented by three groups: (i) RCT participants, (ii) RCT-eligible, and (iii) RCT-non-eligible registry patients. Cumulative incidence curves were used to compare unadjusted outcomes between study groups. For cardiovascular mortality, deaths due to other

causes were treated as competing events. For first HF hospitalization, all-cause deaths were treated as competing events. Then, standardised mortality ratios (SMRs) were used to compare adjusted mortality rates between the trials and the SwedeHF registry population. First, we fitted a Poisson model with 11 prognostic indicators from a validated MAGGIC HF risk score (age, sex, LVEF, NYHA class, serum creatinine, chronic obstructive pulmonary disease (COPD), diabetes, systolic blood pressure, body mass index (BMI), HF duration, smoking status) in a stepwise manner to the trial-eligible SwedeHF patients' data.[20,21] Next, the model with the derived β coefficients was applied to each trial to estimate each individual's expected mortality, which was then summed across all participants to derive total expected mortality counts. The observed mortality count for each trial was divided by the expected mortality count to give the SMRs. An SMR value > 1 indicated that the observed risk of mortality in a trial was higher than the risk predicted based on SwedeHF patients as the reference population. The SMR was risk-adjusted for 11 prognostic factors to address heterogeneity between the trials. This was considered sufficient adjustment to pool the trials using fixed effect meta-analysis without introducing partial pooling. The corresponding 95% CI was determined using methods described by Breslow and Day.[22] SMRs were not estimated for HF hospitalization because its existing risk prediction models do not have adequate discriminative performance compared to those designed to predict mortality.[23]

For cardiovascular causes of mortality, the Poisson model has taken into account competing risk from other causes of death as every patient's follow-up duration was included in the estimation of the number of events. Rather than predicting cumulative probabilities, the Poisson model gives a prediction of the number of events for each individual which can be summed to obtain the total expected number of events in a trial. Missing data was multiply imputed by chained equations using the mice package in R.[24] The number of imputations was set at 20.[25] Statistical significance was set at 0.05. Statistical analysis was performed using the R statistical software version 3.6.1 (R Core Team, 2019) and Stata SE Version 15 (StataCorp LP, College Station, TX).[26,27]

The largest RCTs (BEAUTIFUL and SHIFT) in this analysis only included patients who were in sinus rhythm and the BEAUTIFUL study included a population who had CAD; therefore, sensitivity analyses were conducted in subsets of registry patients who were (i) in sinus rhythm or (ii) diagnosed with CAD. The fully-adjusted

SMRs from each subset were then compared to the original estimates. A third sensitivity analysis was performed to determine the effects of time period differences between trial and registry data on HF medication prescription.

RESULTS

Study population

Majority of registry patients (56%) were eligible for inclusion in the trials (Figure 1). Compared to the overall registry group, RCT patients were younger (mean 63.6 years vs 72.7 years), less frequently women (22% vs 31%), had longer duration of HF, were more often in LVEF category of 30-39% as opposed to <30% and predominantly in NYHA class II rather than III- IV (Table 1). The baseline characteristics of each registry is provided in Supplementary Table 3.

Hypertension, diabetes, and CAD were more common in the RCT group compared to the overall registry group. However, the proportion of patients with valve disease, stroke, anaemia, COPD, cancer, and coronary revascularisation were markedly lower in the RCT patients. After restricting the registry group to those who would be eligible for inclusion in the RCTs, this RCT-eligible registry group was more similar to the RCT group in NYHA class, serum creatinine, and haemoglobin, but differences in comorbidities largely remained (Table 1). In the selection of trial-eligible patients, the most restrictive inclusion criteria were NYHA class II-IV and the use of ACEI/ARB and ß-blockers while the most restrictive exclusion criterion was cancer (Figure 1).

Use and target doses of cardiovascular medication

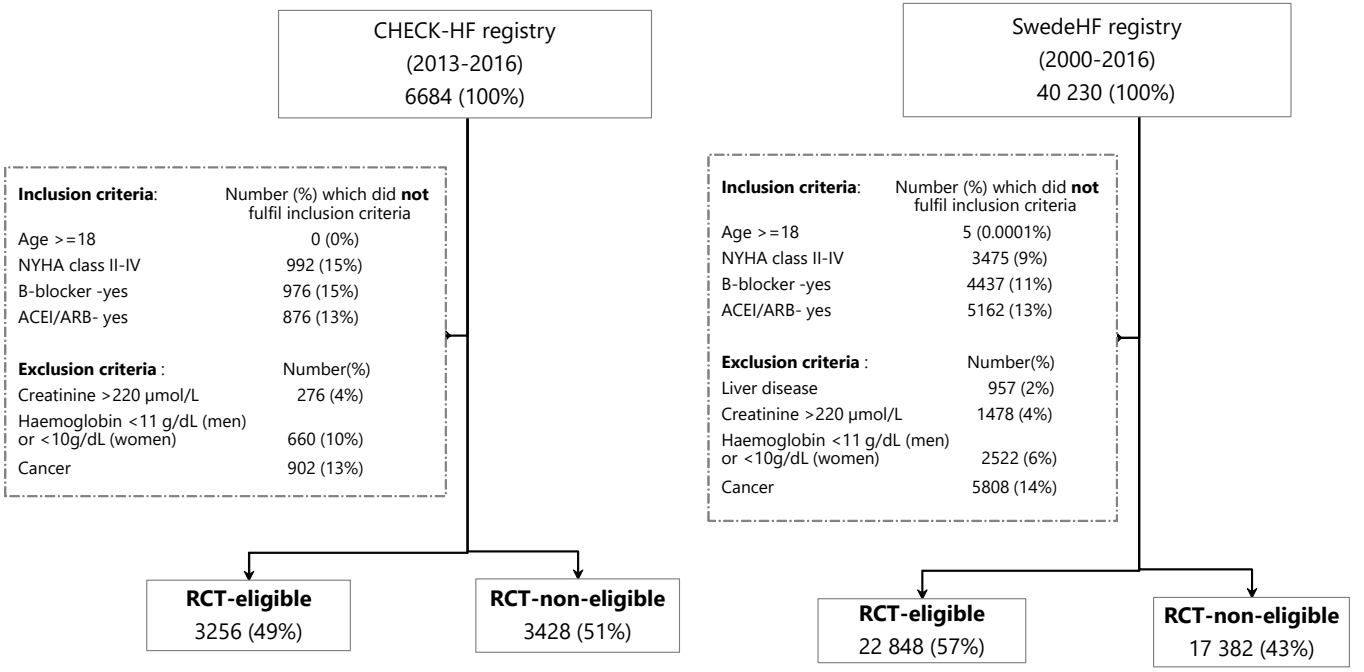
Prescription of medications was higher for antiplatelets, mineralocorticoid receptor antagonists, and statins in the RCTs compared to registry patients. Despite similar proportions in use of ACEI/ ARB (87% vs 90%), more registry than RCT patients received higher doses (≥ 50% of target doses) of these medications (Supplementary table 4). We then restricted the comparison to the same time periods (2005 - 2009) between the 2 largest trials and SwedeHF registry patients and found that the proportion of patients who were given target doses did not differ much from the main findings, which used data from 2001 to 2016 (Supplementary Table 5).

Clinical outcomes at one year

Cumulative incidence curves are shown in the central illustration and Figure 2. All-cause mortality, cardiovascular mortality and first HF hospitalization at one year were lower in the RCTs than in trial-eligible and trial non-eligible registry groups.

There was no remaining difference in all-cause mortality risk between trial and registry patients after adjusting for known HF prognostic factors (fully-adjusted (model 4) SMR 1.04; 95%CI 0.98 – 1.11)) (Central Illustration). However, higher cardiovascular mortality risk persisted in the RCT group compared to trial-eligible registry patients (fully-adjusted (model 4) SMR 1.28; 95%CI 1.20 – 1.37). Age and sex explained most of the mortality difference between patient groups, as reflected in the large shift of SMR between Model 1 (empty model) to Model 2 (with age and sex). Stepwise addition of prognostic factors changed SMR in the same direction but to a lesser degree, as seen in the shift of SMR in Model 2 (with age and sex) to Model 4 (fully adjusted) for all-cause and cardiovascular mortality.

Sensitivity analyses were conducted by estimating SMRs in a subset of patients who were in sinus rhythm and estimates were similar to those obtained in the main results (Supplementary figures 1 and 2).



Percentages of those not included and excluded based on individual criteria does not add up to percentage of non-eligible patients because one patient can be excluded based on one or more criteria
Liver disease status was not recorded in CHECK-HF

Figure 1. Flow chart of selection of RCT-eligible patients based on harmonised eligibility criteria

Table 1. Characteristics of HFrEF patients by RCT and registry groups

		Registry population		RCT vs RCT-eligible	
	RCT population N= 16 922	**RCT- eligible** N= 26 104 (56%)	**RCT-non-eligible** N=20 810 (44%)	**Difference in mean or proportion (99% CI)**	**p-value** [b]
Patient characteristics					
Age (years)	63.6 ± 10.0	71.1 ± 12.6	74.7 ± 13.1	-7.5 (-7.8, -7.2)	***
Women	3663 (22%)	8294 (32%)	6290 (30%)	-10.1% (-11.2%, -9.0%)	***
Body mass index (kg/m^2)	28.3 ± 4.4	27.1 ± 5.7	25.9 ± 6.1	-1.2 (-1.3, -1.1)	***
Systolic blood pressure – mmHg	125.2 ± 13.4	124.6 ± 21.0	124.5 ± 22.7	0.6 (0.1, 1.1)	***
Diastolic blood pressure – mmHg	76.6 ± 8.4	73.7 ± 12.3	72.3 ± 13.4	2.9 (2.6, 3.2)	***
Heart rate – beats per minute	74.4 ± 9.5	74.5 ± 15.9	75.7 ± 17.4	-0.1 (-0.4, 0.2)	
Serum creatinine - µmol/L	99.2 ± 29.5	99.4 ± 37.9	123.4 ± 91.2	-0.2 (-1.1, 0.6)	
Haemoglobin -g/dL	14.1 ± 1.3	13.7 ± 2.1	12.9 ± 2.6	0.4 (0.4, 0.4)	***
Current smoker	2667 (16%)	3370 (15%) [a]	2301 (13%) [a]	1.1% (0.1%, 2.0%)	**
Heart failure severity					
Duration of heart failure -months	42.0 ± 56.4	29.8 ± 61.7	32.9 ± 61.9	12.2 (10.7, 13.7)	***
LVEF categories-no (%)					
<30	5338 (32%)	13 936 (53%)	9751 (47%)	-	***
30-39	11 225 (66%)	12 168 (47%)	11 059 (53%)		
>=40	247 (1%)	-	-		
missing	112(1%)	-	-		
Mean LVEF (%)	31	-	-	-	

Table 1 (continued). Characteristics of HFrEF patients by RCT and registry groups

		Registry population		RCT vs RCT-eligible	
	RCT population N= 16 922	**RCT- eligible** N= 26 104 (56%)	**RCT-non-eligible** N=20 810 (44%)	**Difference in mean or proportion (99% CI)**	**p-value** [b]
NYHA Functional Class – no (%)					
I	3 (0.02%)	0 (0%)	4459 (21%)	-	***
II	10 394 (61%)	14 478 (55%)	7231 (35%)		
III	6422 (38%)	10 623 (41%)	7673 (37%)		
IV	113 (1%)	1003 (4%)	1447 (7%)		
Medical history – no (%)					
Hypertension	11 517(68%)	14 654 (56%)	11 505 (55%)	11.9% (10.7%, 13.2%)	***
Diabetes mellitus	5711 (34%)	7083 (27%)	5649 (27%)	6.6% (5.4%, 7.8%)	***
Coronary artery disease	14 541 (86%)	11 916 (52%) [a]	9497 (55%) [a]	33.8% (32.7%, 34.9%)	***
History of MI	5721 (34%)	8120 (31%)	6776 (33%)	2.7% (1.5%, 3.9%)	***
Atrial fibrillation	449 (38%) [c]	12563 (48%)	10014 (48%)	-10.4% (-14.1% -6.7%)	***
Valvular disease	2009 (12%)	5616 (22%)	5280 (25%)	-10.7% (-11.7%, -9.8%)	***
Stroke/ TIA	1564 (9%)	3220 (14%) [a]	3067 (18%) [a]	-4.8% (-5.7%, -4.0%)	***
Anaemia	588 (3%)	6611 (25%)	9064 (44%)	-21.8% (-22.6%, -21.1%)	***
COPD	1482 (9%)	5084 (19%)	4417 (21%)	-10.7% (-11.6%, -9.9%)	***
Depression	451 (3%)	1117 (5%) [a]	894 (5%) [a]	-2.2% (-2.7%, -1.7%)	***
Cancer	462 (3%)	0 (0%)	6710 (32%)	2.7% (2.4%, 3.1%)	***
Coronary revascularisation					
PCI	1538 (9%)	1994 (8%)	1528 (7%)	-	***
CABG	1029 (6%)	3038 (12%)	2609 (13%)		
PCI + CABG	236 (1%)	2913 (11%)	2020 (10%)		

Table 1 (continued). Characteristics of HFrEF patients by RCT and registry groups

		Registry population		RCT vs RCT-eligible	
	RCT population N= 16 922	**RCT- eligible** N= 26 104 (56%)	**RCT-non-eligible** N=20 810 (44%)	**Difference in mean or proportion (99% CI)**	**p-value** [b]
Clinical outcomes at 1 year					
All-cause mortality	1112 (7%)	2674 (12%) [a]	4482 (26%) [a]	-5.1% (-5.9%, -4.4%)	***
Cardiovascular mortality	1005 (6%)	2026 (9%) [a]	3114 (18%) [a]	-2.9% (-3.6%, -2.3%)	***
First HF hospitalization	1399 (8%)	5544 (24%) [a]	4310 (25%) [a]	-16.0% (-16.9%, -15.1%)	***
Cardiovascular medications at baseline					
ACEI/ ARB [d]	15 251 (90%)	26 104 (100%)	14 773 (71%)	-	-
β -blocker [d]	14 808 (88%)	26 104 (100%)	15 392 (75%)	-	-
MRA	7294 (43%)	10 275 (40%)	6880 (33%)	3% (2%, 5%)	***
Diuretic	12 120 (72%)	20 697 (79%)	16 379 (79%)	-8% (-9%, -7%)	***
Antiplatelet	13 208 (78%)	12 329 (47%)	9788 (47%)	31% (30%, 32%)	***
Digitalis	2500 (15%)	4447 (17%)	3002 (14%)	-2% (-3%, -1%)	***
Statins	11 231 (66%)	13 995 (54%)	9674 (47%)	13% (11%, 14%)	***

Values are expressed as mean standard deviation or number (%)

*p<0.05, **p<0.01, ***p<0.001

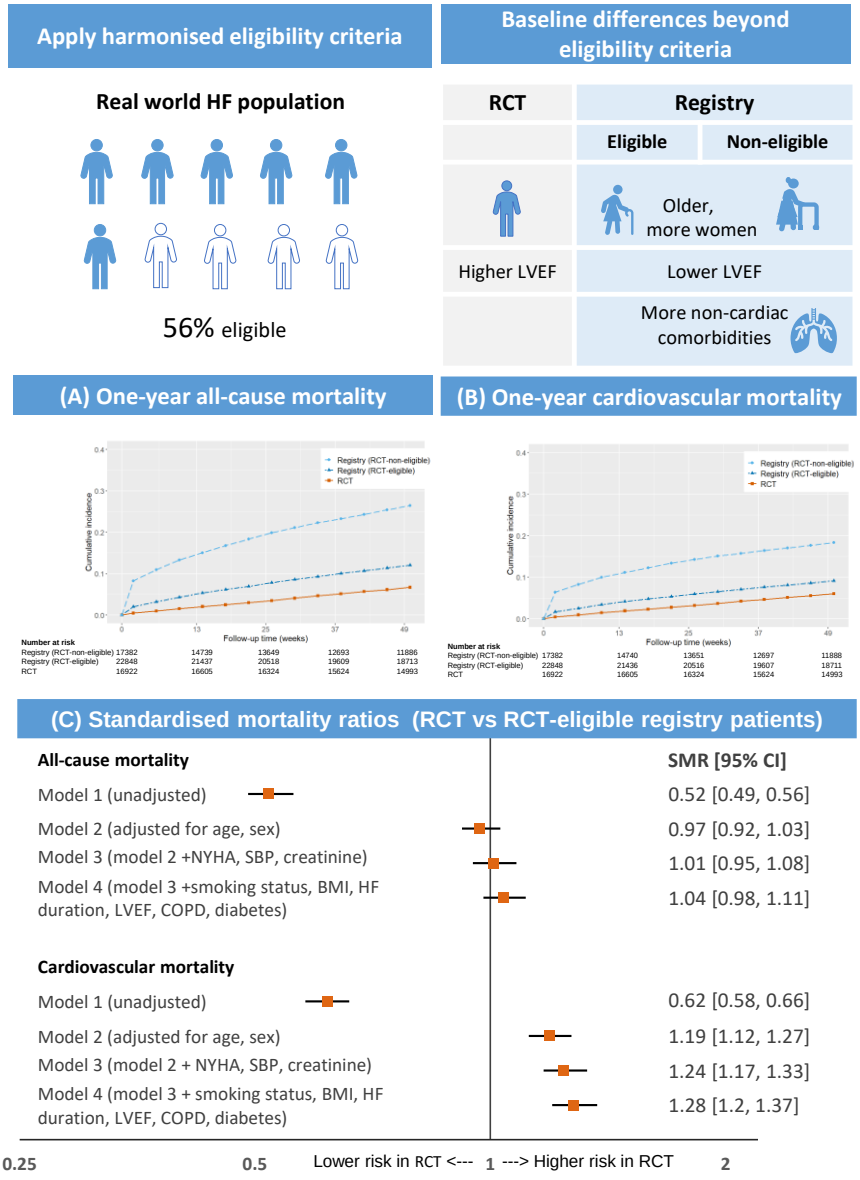
a. data from SwedeHF only

b. comparison between RCT and registry (RCT-eligible) population (independent t-test for continuous and $\chi 2$ -test for categorical variables)

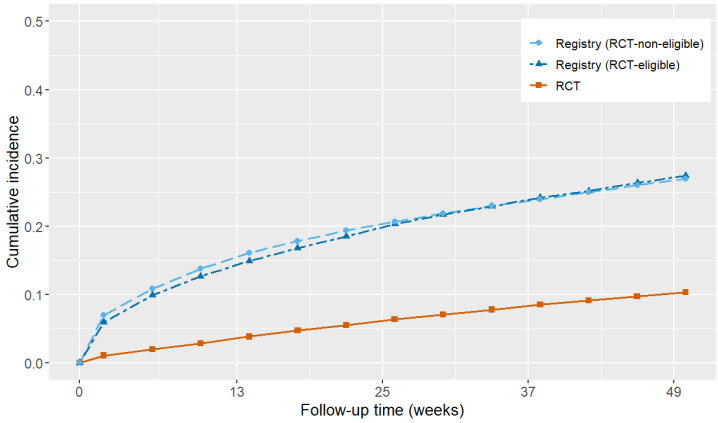
c. RCT data only from CONFIRM, FAIR HF and PANTHEON

d. Statistical comparisons were not done for ACEI/ ARB and β-blocker because these treatments were part of the criteria for selecting RCT-eligible registry patients

Percentages may not add up to 100% due to rounding. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CABG, coronary artery bypass graft; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack



Central illustration. Cumulative incidence and case-mix adjusted standardised mortality ratios for all-cause and cardiovascular mortality at one year. (A) Cumulative incidence for all-cause mortality between RCT and registry patients. (B) Cumulative incidence for cardiovascular mortality between RCT and registry patients. (C) Standardised mortality ratios (SMR) for all-cause and cardiovascular mortality with stepwise adjustment for HF prognostic factors. Pooled SMRs estimated from 5 trials with their 95% CI were reported.



Number at risk					
Registry (RCT-non-eligible)	17382	12802	11320	10242	9334
Registry (RCT-eligible)	22848	18911	17179	15766	14583
RCT	16922	16387	15895	15151	14459

Figure 2. Cumulative incidence curves for first HF hospitalization at 1 year by (i) RCT participants, (ii)RCT-eligible and (iii) RCT-non-eligible registry patients

DISCUSSION

The present study has individual patient data of over 62 000 patients from five clinical trials and two observational HF registries, which allowed direct and adjusted comparisons on patient characteristics for both all-cause and cause-specific mortality. Overall, we found that over half of patients in the registries met the most commonly used in- and ex-clusion criteria for trial enrolment. Unadjusted survival was markedly lower in registries than trials. However, after adjusting for case-mix, all-cause mortality rates were comparable between the trials and registries while cardiovascular mortality occurred more frequently in the trial participants compared to registry patients.

We identified a higher proportion of trial-eligible patients compared to previous studies on patients with acute decompensated HF and HF with reduced and preserved ejection fraction: 56% vs. 13 % to 42%.[8,28,29] Furthermore, the percentage of trial-eligible registry patients who were given at least 50% target doses of HF medications were slightly higher than in RCTs. This higher proportion compared to previous reports could be explained at least in part by extensive heart failure programs and nurse-led up-titration of disease-modifying therapies in the

Netherlands and Sweden. Also, data in the registries were from more recent years than the trials, thus reflecting more contemporary prescribing practices. Accordingly, we would expect background therapies in newer HF trials to be at a higher rate than the ones described here. Therefore, our findings, along with other recent studies in acute HF suggest that the gap in HF guideline-adherent treatment between trial and real-world patients is narrowing.[6,30]

The differences observed between trial participants and trial-eligible registry patients highlight other factors besides eligibility criteria that influence patient selection in RCTs. Physicians intuitively recruit patients who are deemed less likely to drop out to ensure low attrition rates which retain high internal validity.[31–33] Older patients and those with comorbidities are not always physically or mentally able to comply and finish the treatment protocol due to frailty, low mobility and increased risk for adverse events.[7,34] Women with HF tend to be older and are less likely to participate due to perceived harm from clinical studies, transportation difficulties, or constraints from a caregiving role.[33,35,36] Consequently, the additional criteria introduced by investigators alongside the eligibility criteria consistently cause underrepresentation of older patients, those with comorbidities and women in CV trials..[37] However, expanding the study population to include these groups would increase the cost of already expensive HF trials, and other solutions to improve generalizability that have been proposed include individual participant data meta-analysis, proper reporting of subgroup analysis, registry-based trials or comparative effectiveness studies.[38–40] The growing trend to conduct RCTs as site-less or direct-to-patient studies may reduce this bias in the future.

We have shown, by direct comparisons between study groups that the risk of mortality and HF hospitalization was lowest in the trial population. However, after accounting for known prognostic factors for survival in HF, differences in survival between trial and registry patients disappeared. In fact, age and sex combined explained the largest variation in standardised mortality ratios between trials and registries. This observation is evident for both all-cause and cardiovascular mortality and highlights their important contribution on the generalizability of HF trials.

Taken together, it seems that differences in overall survival between HF trials and registries behave predictably and could be addressed by clinical variables which are readily available in daily clinical practice. Although well-accepted, we have demonstrated for the first time that there are increased cardiovascular mortality rates

in the HF trial participants compared to trial-eligible registry patients, as high up to 30% even after adjustment for prognostic factors. From a drug developer and/or regulatory perspective, prognostic enrichment strategies were advocated and used in many cardiovascular trials to identify patients who a have higher likelihood of cardiovascular events.[32] Additionally, excluding patients with other comorbidities in these trials could lead to lower competing risks of death from non-cardiovascular causes. On a broadly similar note, trial-eligible registry patients selected for the PARADIGM-HF trial criteria had higher risk of both cardiovascular and non-cardiovascular mortality compared to non-eligible registry patients.[41] From the clinicians' perspective, it is important to be aware that half of patients were ineligible, and that even among trial-eligible patients, residual differences between cardiovascular and non-cardiovascular outcomes persists.

Strengths and limitations

The strength of this study lies in the large sample sizes from both trial and observational datasets. Direct access to individual patient data also enabled the reporting of case-mix-adjusted differences in outcomes between trials and registry. There are also several limitations to this study. First, we applied a harmonised set of criteria which were common across the trials based only on data that were also available from the registries. There was not sufficient depth in the data from the registries to assess many of the eligibility criteria such as worsening HF in the past 12 months, scheduled coronary revascularisation within 3 months or severe valve disease. Also, not all criteria per RCT have been considered but only the most common ones. For these reasons, the percentage of patients eligible for trial inclusion is likely overestimated. The trials included in this study were a convenient sample based on data accessibility; thus, it can be difficult to infer these findings to other HF trials. Secondly, a large proportion of trials patients came from two RCTs which excluded patients with atrial fibrillation (BEAUTIFUL and SHIFT), which might have impacted the results. However, we believe that this impact is not substantial, as supported by sensitivity analyses (Supplementary figures 1 and 2). Although the trials evaluated here were not the most recent HFrEF trials, we do not expect large changes in patient and clinical characteristics among those enrolled in trials then and now. This is supported by a baseline characteristics comparison with DAPA-HF and PARADIGM-HF, which showed comparable patient characteristics in terms of mean

age, percentage of women, percentage in NYHA class III/IV and mean LVEF, except for percentage with atrial fibrillation which was lower in this study.[42] It is also necessary to note that, although registry patients are a fair representation of real-world patients, there are likely to be some differences in characteristics and treatment practices between patients who were and were not enrolled in the registries. We also acknowledge that the trial and real-world populations differed on geographical location, healthcare systems and time of data collection.[43]

CONCLUSION

In summary, over half of patients in registries met the most commonly used in- and ex- clusion criteria for potential trial enrolment. In terms of generalisability, age and sex were the main drivers of differences in clinical outcomes between HF trials and observational HF registries. As expected, HF trial participants showed higher residual cardiovascular mortality rates after correction for case mix.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Characteristics, inclusion and exclusion criteria of trials

Study name	**BEAUTIFUL**	**CONFIRM-HF**	**FAIR-HF**	**PANTHEON**	**SHIFT**
Phase	III	IV	III	II	III
Drug	Ivabradine	Ferric carboxymaltose	Ferric carboxymaltose	Neladenosone bialanate	Ivabradine
Year	2005-2008	2011 - 2014	2007-2009	2017-2018	2006-2010
Number of patients	10917	304	456	427	6505
Duration of follow-up	12 months	52 weeks	40 weeks	26 weeks	30 months
Inclusion Criteria					
	Male or female patient of any ethnic origin, non-diabetic (type I or II) aged ≥ 55 years, or diabetic (type I or II) aged ≥ 18 years	At least 18 years of age.	At least 18 years of age and signed written informed consent.	Men or women aged 18 years and older	Male or female patients aged ≥ 18 years

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	Evidence of CAD documented by - previous MI (at least 6 months ago and confirmed by ECG demonstrating abnormal Q waves in 2 contiguous leads and/or biochemical markers of cardiac necrosis) - or previous (at least 6 months ago) percutaneous or surgical coronary revascularisation - or angiographic evidence of at least 50 % narrowing of one or more major coronary vessels In stable condition (for at least 3 months) with regards to angina and/or heart failure symptoms and on appropriate and stable doses, for at least 1 month, of conventional	Subjects with stable CHF (NYHA II-III functional class) Brain natriuretic peptide >100 pg/mL and/or N-terminal-pro-brain natriuretic peptide >400 pg/mL at the screening visit.	In NYHA II-III functional class due to stable symptomatic chronic heart failure (CHF), and all of the following: a. Two weeks without cardiac hospitalization. b. Patients in NYHA II must have had an acute care admission or emergency room visit for worsening of heart failure within 24 months prior to start of treatment.	Diagnosis of chronic heart failure, NYHA class II-IV, One of the following (or both): A) Worsening chronic heart failure requiring hospitalization or an unscheduled outpatient visit in the last 3 months, both requiring initiation or intensification of heart failure therapy and with either: i)BNP ≥ 100 pg/mL or NT-proBNP ≥400 pg/mL (sinus rhythm) or ii) BNP ≥ 300 pg/mL or NT-proBNP ≥1200 pg/mL (atrial fibrillation) AND/OR B) at any time in the past 4 weeks one of: i)BNP ≥ 300 pg/mL or NT-proBNP ≥ 1200 pg/mL (sinus rhythm)	Symptomatic CHF i.e., NYHA class II, III or IV for at least 4 weeks prior to selection In stable clinical condition with regards to CHF symptoms for at least 4 weeks prior to selection. All aetiologies of CHF included, except for congenital heart disease and for severe aortic or mitral stenosis, or severe aortic regurgitation or severe primary mitral regurgitation Documented hospital admission for worsening heart failure within 12 months before selection

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	LVEF equal to 39% or lower on a recently performed measurement (in the previous 4 weeks) from a two-dimensional echocardiography and left ventricular dilatation on an echocardiographically measured short-axis internal dimension at end diastole greater than 56 mm (exam performed in the previous 4 weeks).Documented sinus rhythm and HR of 60 beats per minute or more on a recent (within 24 hours) resting standard 12-lead ECG	LEVF ≤45% (value within 3 months of planned date of randomization).	LVEF ≤ 40% for patients in NYHA II and ≤ 45% in NYHA III as assessed according to local methodology by 2-D echocardiography, radionuclide ventriculography, cardiac magnetic resonance imaging, or X-ray contrast ventriculography within 6 months prior to start of treatment. For patients treated with beta-blockers or with cardiac resynchronisation, LVEF assessment for eligibility must be performed at least 12 weeks after stable beta-blocker therapy or device implantation.	LVEF ≤ 35%assessed by any imaging modality within 6 months prior to run in: if several values are available the last assessment of LVEF should be ≤ 35%.	LVEF ≤ 35% as measured and documented within the previous 3 months (in a stable condition) by echocardiography, radionuclide ventriculography, magnetic resonance imaging, cardiac angiography or computed tomography angiography.Documented sinus rhythm and HR ≥ 70 bpm on a recent (within 24 hours) resting standard 12-lead ECG

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	Background cardiovascular treatment had to be considered optimal by the investigator, and should, in principle, include betablockers, statins, ACEI or ARB, and antiplatelet drugs	On optimal background therapy for at least 4 weeks with no dose changes of HF drugs during the last 2 weeks (with the exception of diuretics). In general, optimal pharmacological treatment should include an ACEI or ARB and a beta-blocker unless contraindicated or not tolerated and diuretic if indicated.	On optimal conventional therapy (optimal pharmacological treatment which includes a diuretic, a beta-blocker, and/or an ACEI or ARB as determined by the investigator, unless contraindicated or not tolerated). No dose changes of heart failure drugs during the last 2 weeks (with the exception of diuretics). No introduction of a new heart failure drug class during the last 4 weeks.		Optimized and unchanged CHF medications or dosages, for at least 4 weeks prior to selection.
	Haemoglobin≥ 110 g/L (in males) or ≥100 g/L (in females) [a]		Screening haemoglobin (Hb) at least 9.5 g/dL but below or equal to 13.5 g/dL (average of 2 haemoglobin concentrations as measured locally by HemoCue® analyzer	Haemoglobin ≥ 10 g/dL within 3 months prior to randomization. If several values are available, the latest result should be used. [a]	Serum haemoglobin ≥ 110 g/L (≥11 g/dL) [a]

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
		Screening serum ferritin <100 ng/mL OR 100-300 ng/mL with transferrin saturation <20%.	Screening ferritin below 100 µg/L, or below 300 µg/L when transferrin saturation (TSAT) is below 20% (re-screening is possible after 4 weeks for patients with borderline higher ferritin concentrations or borderline TSAT percentage if the investigator feels that levels might drop below cut-off in the near future.		
			Resting blood pressures less than or equal to 160 mm Hg (systolic) and less than or equal to 100 mm Hg (diastolic at the disappearance of sounds, Korotkoff phase V).		
			Adequate veins for repeated blood sampling and intravenous administration of investigational drug.		
			Negative pregnancy test and use of adequate contraceptive methods for women of childbearing potential.		
		Capable of completing the 6MWT.	Capable of completing the 6 MWT.		

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
			Exclusion criteria		
	Unstable cardiovascular condition History of stroke or cerebral transient ischaemic attack within the preceding 3 months Valvular disease likely to require surgery within the next 3 years Current severe symptoms of heart failure (NYHA class IV) Patient with recent (less than 6 months) MI or coronary revascularisation Patient scheduled for revascularisation (PCI or CABG)Implanted pacemaker or implantable cardioverter defibrillator Sick sinus syndrome, sinoatrial block, congenital long QT, complete atrio-ventricular blockadePatient with transplanted heart	Unstable angina pectoris as judged by the investigator; Severe valvular or left ventricular outflow obstruction disease needing intervention Atrial fibrillation/flutter with a mean ventricular response rate at rest >100 beats per minute. Acute myocardial infarction or acute coronary syndrome, transient ischaemic attack or stroke within the last 3 months prior to randomization Coronary-artery bypass graft, percutaneous intervention or major surgery, including thoracic and cardiac surgery, within the last 3 months.	Unstable angina pectoris as judged by the investigator, Clinically significant uncorrected valvular disease or left ventricular outflow obstruction Obstructive cardiomyopathy Poorly controlled fast atrial fibrillation or flutter Poorly controlled symptomatic brady- or tachyarrhythmias. Acute myocardial infarction or acute coronary syndrome, transient ischaemic attack or stroke within the last 3 months. Coronary-artery bypass graft, percutaneous intervention or major surgery, including thoracic and cardiac surgery, within the last 3 months.	Occurrence of any of the following within 3 months prior to randomization:- Myocardial infarction- Hospitalization for unstable angina- Stroke or transient ischemic attack- Coronary artery bypass graft (CABG) Percutaneous coronary intervention (PCI)- Implantation of a cardiac resynchronization therapy device (CRTD) Carotid angioplastyPCI, CABG or implantation of a CRTD planned between randomizationand end of study Any cause of chronic heart failure other than ischemic cardiomyopathy and idiopathic dilated cardiomyopathy Acute de-novo heart failure Known clinically significant persistent coronary ischemia based on medical history, pre-existing or current exercise testing	Unstable condition within the previous 4 weeks History of stroke or transient cerebral ischaemia within the previous 4 weeks. Severe aortic or mitral stenosis, or severe aortic regurgitation or severe primary mitral regurgitation Scheduled surgery for valvular heart disease Active myocarditis Congenital heart diseases Significant cardiovascular condition, including the occurrence of a pre-specified event since the informed consent signature, change in heart failure background therapy or dosage, or use of intravenous inotropic therapies Recent (less than 2 months) myocardial or coronary revascularisation Scheduled coronary revascularisation (PCI or CABG)

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
				Clinically relevant permanent or intermittent atrioventricular-block > grade II in patients without a permanent pacemaker or ICD / CRTD Known clinically relevant ventricular arrhythmias (sustained ventricular tachycardia, ventricular flutter or fibrillation) within 3 months prior to consent based on either medical history or implantable cardioverter defibrillator Severe valvular disease with indicated or planned valve repair / anticipated heart transplantation and / or implantation of a ventricular assist device	Cardiac resynchronisation therapy started within the previous 6 months Pacemaker with atrial or ventricular pacing (except bi-ventricular pacing) > 40 % of the time, or with a stimulation threshold at the atrial or ventricular level ≥ 60 bpm Permanent atrial fibrillation or flutter Sick sinus syndrome, sinoatrial block, 2nd and 3rd degree atrio-ventricular block History of symptomatic or sustained (≥ 30 sec) ventricular arrhythmia unless a cardioverter defibrillator was implanted Any cardio defibrillator shock experienced within the previous 6 months. Familial history or congenital long QT syndrome or treated with selected QT prolonging products Previous cardiac transplantation or on list for cardiac transplantation

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	Known severe renal disease Serum creatinine > 200 micromoles/L	Renal dialysis (previous, current or planned within the next 6 months).	Immunosuppressive therapy or renal dialysis (current or planned within the next 6 months).	Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 calculated by Modification of Diet in Renal Disease formula within 3 months prior to randomization. If several values are available, thelatest result should be used.	Known severe renal disease (serum creatinine > 220 µmol/L)
	Known carriers of hepatitis B surface antigen or hepatitis C virus antibodies Known severe liver disease ALT or ALT > 3 times upper normal values	Chronic liver disease (including active hepatitis) and/or screening alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range. Subjects with known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity	Chronic liver disease and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) above three times the upper limit of the normal range.	Hepatic insufficiency classified as Child-Pugh B or C, or any of the following: - Primary biliary cirrhosis (PBC) - Primary sclerosing cholangitis - PBC-autoimmune hepatitis overlap syndrome	Known carriers of hepatitis B surface antigen or hepatitis C virus antibodies Known moderate or severe liver disease (Child-Pugh score > 7) ALT and/or AST > 3 times the upper normal values

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	Any serious disease likely to interfere with the conduct of the study Patient for whom life expectancy is shorter than the study duration for a non-cardiovascular illness (e.g. cancer)	Known active bacterial infection. Clinical evidence of current malignancy with exception of basal cell or squamous cell carcinoma of the skin, and cervical intraepithelial neoplasia. Currently receiving systemic chemotherapy and/or radiotherapy.	Known active infection, CRP > 20 mg/L, clinically significant bleeding, active malignancy	Any condition or therapy, which would make the patient unsuitable for the study, or life expectancy less than 12 months (e.g., active malignancy)	Any serious disease likely to interfere with the conduct of the study or any non-cardiac disease (e.g., cancer) judged likely to limit 3-years survival
	Known carriers of HIV antibodies	Subjects with known seropositivity to HIV	Known HIV/AIDS.		Known carriers of HIV antibodies
				Requirement of any of the following 48 hours prior to randomization:- Intravenous vasodilating drugs (e.g., nitrates, nitroprusside), IV natriuretic peptides (e.g., nesiritide, carperitide), IV positive inotropic agents, IV diuretics, IV antibiotics,mechanical support (e.g., intra-aortic balloon pump, endotrachealintubation, mechanical ventilation, or any ventricular assist device)	

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
				Sustained systolic blood pressure ≤ 90 mmHg and / or signs and symptoms of hypotension prior to randomization	
	Severe or uncontrolled hypertension at the time of selection (SBP > 180 mmHg or DBP > 110 mmHg)			Sustained systolic blood pressure ≥ 160 mmHg	Severe or uncontrolled hypertension (sitting SBP > 180 mmHg or sitting DBP > 110 mmHg) Sitting SBP < 85 mm Hg or current symptomatic hypotension
				Sustained bradycardia with heart rate < 50 beats/minute or tachycardia with heart rate > 100 beats/minute prior to randomization	
				Severe pulmonary disease with any of the following: - Requirement of continuous (home) oxygen or - History of chronic obstructive pulmonary disease ≥ GOLD III or - Bronchial asthma	

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
		Body weight ≤35 kg.		Body mass index (BMI) > 40 kg/m2 at randomization or a history of poor quality LVEF measurement by echocardiography	
	Patients requiring the following medications: macrolide antibiotics, cyclosporin, gestodene, antiretroviral drugs or azole antifungals such as ketoconazole	Vitamin B12 and/or serum folate deficiency. If deficiency corrected subject may be rescreened for inclusion. History of acquired iron overload. History of erythropoietin stimulating agent, IV iron therapy, and/or blood transfusion in previous 6 weeks prior to randomization. Subject at an immediate need of transfusion or haemoglobin ≥15 g/dL.	Vitamin B12 and/or serum folate deficiency according to the central laboratory History of acquired iron overload. History of erythropoietin, IV or oral iron therapy, and blood transfusion in previous 12 weeks and/or such therapy planned within the next 6 months.	Concomitant use of any of the following therapy that cannot be discontinued: - Potent CYP3A4 inhibitors or inducers or strong CYP2C8 inhibitors - Theophylline - Drugs that are mainly metabolized by UGT1A1 (irinotecan) Respective substances must be stopped at least 7 days before randomization.	

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	Women who are pregnant, breast-feeding or women of childbearing potential not using estro-progestative or progestative or intra-uterine contraception or women using estro-progestative or intra-uterine contraception but who consider stopping it during the planned duration of the study	Subject of child-bearing potential who is pregnant (e.g., positive human chorionic gonadotropin test) or is breast feeding. Subject is not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of study medication.	Pregnancy or lactation.	Women of childbearing potential (women are considered of childbearing potential if they are not surgically sterile or postmenopausal, defined as amenorrhea for > 12 months)	Women who are pregnant, breast-feeding or women of childbearing potential not using estro-progestative or progestative or intra-uterine contraception or women using estro-progestative or intra-uterine contraception but who consider stopping it during the planned duration of the study
	Unlikely to cooperate in the study Legal incapacity or limited legal incapacity	Subject will not be available for all protocol specified assessments. Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures.	Inability to fully comprehend and/or perform study procedures in the investigator's opinion.		Unlikely to cooperate in the studyLegal incapacity or limited legal incapacity
	Known alcohol or drug abuse			Heavy alcohol consumption or the use of illicit drugs that, in the opinion of the investigator, may interfere with the patient's safety and / or compliance	Known alcohol or drug abuse

Supplementary table 1 (continued). Characteristics, inclusion and exclusion criteria of trials

Study name	BEAUTIFUL	CONFIRM-HF	FAIR-HF	PANTHEON	SHIFT
	Participation in a drug or device trial within the previous 30 days.	Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study, or subject is receiving other investigational agent(s). Exercise training program(s) in the 3 months prior to screening or planned in the next 6 months.	Participation in another clinical trial within previous 30 days and/or anticipated participation in another trial during this study.	Use of other investigational drugs. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s)	Participation in another drug or device trial at the same time or within 5 drug half-lives of the investigational drug, or within the time legally required by regulatory authorities, whichever are longer) or already enrolled in the study
		Oral iron therapy at doses >100 mg/day in previous 1 week prior to randomization.			
	Known hypersensitivity to ivabradine	Subject has known sensitivity to any of the products to be administered during dosing.	Known hypersensitivity to Ferinject®.	Known allergies or hypersensitivities to adhesives or hydrogel	Known hypersensitivity to ivabradine
	Known hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption				Known hereditary problems of lactose intolerance, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

a. Threshold are reversed when moved from exclusion to inclusion criteria to standardise across trials

Supplementary table 2. Target doses of heart failure medication

<table>
<tr><td colspan="2">Anti-aldosterone agent (Mineralocorticoid receptor antagonist)
Eplerenone 50mg
Spironolactone 25mg</td></tr>
<tr><td>Angiotensin-converting enzyme inhibitor (ACEI)
Captopril 150mg
Cilazapril 5mg
Enalapril 20mg
Fosinopril 40mg
Lisinopril 40mg
Perindopril 8mg
Quinapril 40mg
Ramipril 10mg
Trandolapril 4mg</td><td>Angiotensin-II receptor blocker (ARB)
Candesartan 32mg
Eprosartan 800mg
Irbesartan 300mg
Losartan 150mg
Telmisartan 80mg
Valsartan 320mg</td></tr>
<tr><td colspan="2">Angiotensin receptor- Neprilysin inhibitor (ARNI)
Sacubitril/Valsartan 194mg/206mg</td></tr>
<tr><td colspan="2">Beta-blocker
Atenolol 100mg
Bisoprolol 10mg
Carvedilol 50mg
Labetolol 600mg
Metoprolol succinate 200mg
Metoprolol tartrate 150mg
Nebivolol 10mg
Pindolol 20mg
Propranolol 240mg
Sotalol 320mg
Timolol 20mg</td></tr>
<tr><td colspan="2">I^f channel inhibitor
Ivabradine 15mg</td></tr>
</table>

Supplementary table 3. Baseline characteristics by registry

	CHECK-HF	SwedeHF
Patient characteristics		
Age (years)	71.8 ±12.2	72.8 ±12.9
Women	2289 (34%)	12296 (31%)
Body Mass Index (kg/m^2)	27.2 ±5.4	26.4 ±6.7
Systolic blood pressure – mmHg	124.4 ±21.1	124.6 ±22
Diastolic blood pressure – mmHg	71.1 ±11.6	73.4 ±13.3
Heart rate – beats per minute	71.9 ±14.4	75.6 ±18.1
Serum creatinine -µmol/L	111 ±73.4	109.9 ±64
Haemoglobin -g/dL	13 ±3.5	13.4 ±1.8
Current smoker	-	5671 (14%)
Heart failure aetiology & severity		
Duration of heart failure (months)	60.5 ±74.1	26.3 ±45.8
LVEF categories-no (%)		
<30	3647 (55%)	20040 (50%)
30-39	3037 (45%)	20190 (50%)
NYHA Functional Class – no (%)		
I	992 (15%)	3467 (9%)
II	3847 (58%)	17862 (44%)
III	1722 (26%)	16573 (41%)
IV	123 (2%)	2328 (6%)
Medical history – no (%)		
Hypertension	2579 (39%)	23580 (59%)
Diabetes mellitus	1943 (29%)	10789 (27%)
Coronary artery disease	-	21413 (53%)
History of MI	2156 (32%)	12740 (32%)
Valvular disease	960 (14%)	9936 (25%)
Stroke/ TIA	-	6287 (16%)
Anaemia	2701 (40%)	12974 (32%)
COPD	1210 (18%)	8291 (21%)
Depression	-	2011 (5%)
Cancer	902 (13%)	5808 (14%)
Coronary revascularisation		
PCI	1363 (20%)	2159 (5%)
CABG	1127 (17%)	4520 (11%)
PCI + CABG	311 (5%)	4622 (11%)

Supplementary table 4. Number and percentage of patients who received <50% or >= 50% target doses of heart failure medication by the 4 comparison groups

		Registry population		
	RCT population N= 16922	**All** N=46914 (100%)	**RCT-eligible** N= 26104 (56%)	**RCT-non-eligible** N=20810 (44%)
ACEI/ARB				
>0 - <50%	5417(37%)	13196(33%)	7693(30%)	5503(38%)
>=50%	9242(63%)	27230(67%)	18171(70%)	9059(62%)
Beta-blocker				
>0 - <50%	7096(50%)	15954(39%)	9474(36%)	6480(42%)
>=50%	6968(50%)	25502(61%)	16610(64%)	8892(58%)
Aldosterone antagonist				
>0 - <50%	40(1%)	80(0%)	46(0%)	34(1%)
>=50%	5051(99%)	17112(100%)	10226(100%)	6846(99%)

Values are expressed as number (%)

Denominator for target doses include only those with dose information available, and for individual drugs which have designated target doses according to the ESC guidelines

Percentages may not add up to 100% due to rounding. ACE, angiotensin- converting enzyme inhibitor; ARB, angiotensin-II receptor blocker

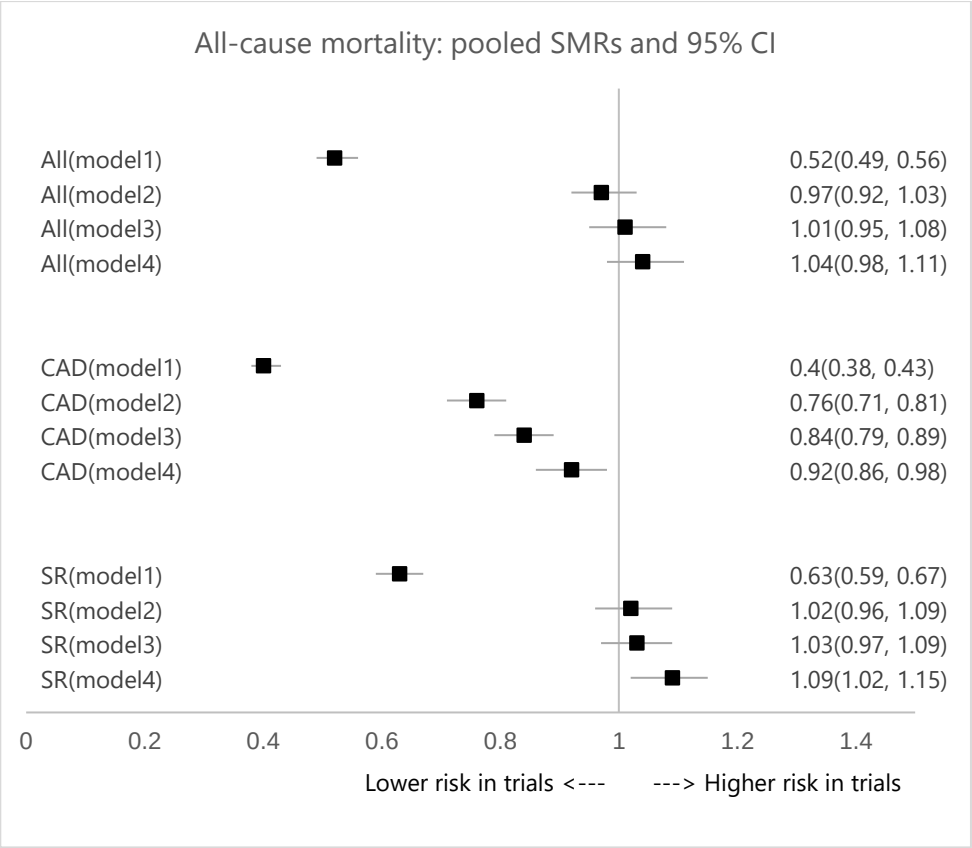
Supplementary table 5. Number and percentage of patients who received <50% or >= 50% target doses of heart failure medications: comparing target doses between the overall study period and after restricting to only time period coinciding with the two largest trials

	RCT		SwedeHF registry			
			all (2001 - 2016)		2005-2009[a]	
n	16922		40230	(100%)	15025	(37%)
Target doses of heart failure medications– no (%)						
ACEI						
>0 - <50%	4313	33%	8455	28%	2399	23%
>=50%	8567	67%	22056	72%	7817	77%
ARB						
>0 - <50%	1181	61%	5150	48%	1620	54%
>=50%	761	39%	5537	52%	1386	46%
ACEI/ARB						
>0 - <50%	5417	37%	13196	33%	3814	30%
>=50%	9242	63%	27231	67%	9025	70%
Beta-blocker						
>0 - <50%	7096	50%	15966	39%	5039	39%
>=50%	6968	50%	25499	61%	7995	61%

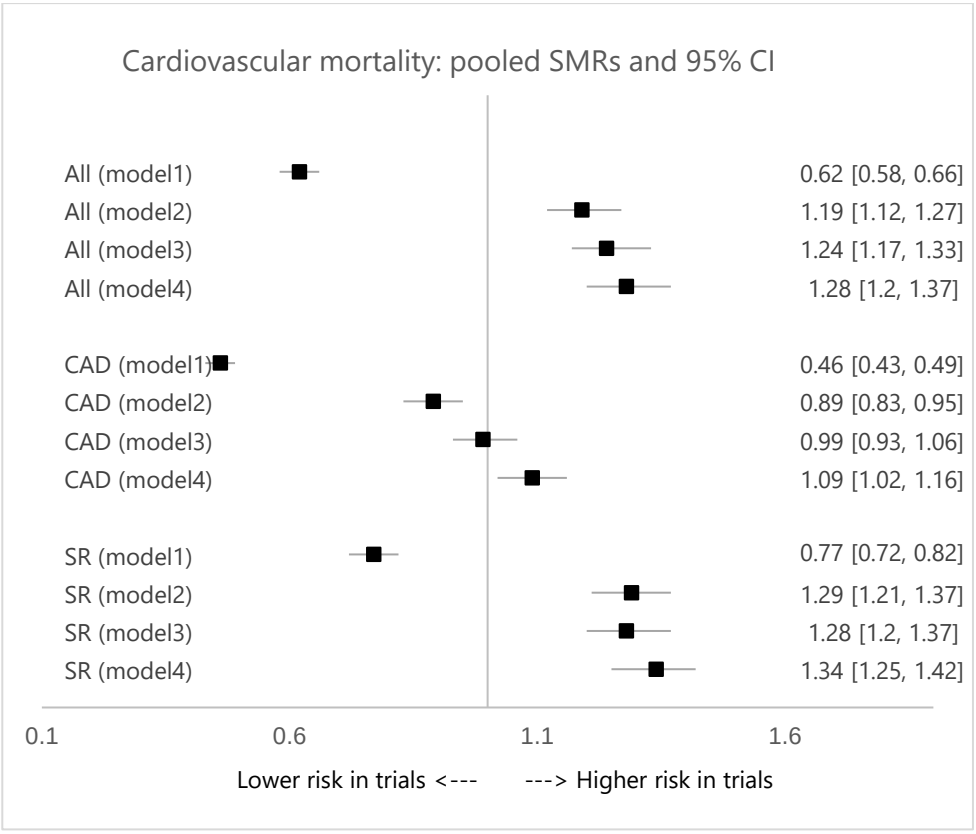
Values are expressed as number (%)

a- time period which coincides with the conduct of the two largest trials in this study

ACE, angiotensin- converting enzyme inhibitor; ARB, angiotensin-II receptor blocker



Supplementary figure 1. Standardised mortality ratios (SMR) for all-cause mortality with stepwise addition of HF prognostic factors for (a) all HFrEF patients, (b) only patients with coronary artery disease (CAD) and (c) only patients who were in sinus rhythm (SR). Model 1 is an empty model and model 2 includes age and sex. Model 3 includes the previous model with systolic blood pressure, serum creatinine and NYHA class. Model 4 includes age, sex, NYHA class, systolic blood pressure, serum creatinine, smoking status, BMI, duration of heart failure, haemoglobin, COPD and diabetes status. Pooled SMRs estimated from 5 trials with their 95% CI were reported



Supplementary figure 2. Standardised mortality ratios (SMR) for cardiovascular mortality with stepwise addition of HF prognostic factors for (a) all HFrEF patients, (b) only patients with coronary artery disease (CAD) and (c) only patients who were in sinus rhythm (SR). Model 1 is an empty model and model 2 includes age and sex. Model 3 includes the previous model with systolic blood pressure, serum creatinine and NYHA class. Model 4 includes age, sex, NYHA class, systolic blood pressure, serum creatinine, smoking status, BMI, duration of heart failure, haemoglobin, COPD and diabetes status. Pooled SMRs estimated from 5 trials with their 95% CI were reported

Chapter 2.2

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

Yvonne Mei Fong Lim
Folkert W Asselbergs
Ayoub Bagheri
Spiros Denaxas
Wan Ting Tay
Carolyn Su Ping Lam
Adriaan A Voors
Stefan Koudstaal
Diederick E Grobbee
Ilonca Vaartjes

Submitted

ABSTRACT

Background

Decisions on eligibility criteria for randomized trials rely on clinical experience and lessons from prior trials. With growing computing capabilities and data access, possibilities have opened for data-guided criteria selection. This study aims to evaluate the magnitude and predictors of clinical trial and registry mismatch based on trial inclusion and exclusion criteria.

Methods

Interventional phase 3 trials registered for heart failure (HF) in ClinicalTrials.gov as of end 2021 were identified. Natural language processing was used to extract and structure the eligibility criteria for quantitative analysis. These criteria were ranked by frequency. The most common ones were applied to estimate eligibility, as a proportion of registry patients. Patient eligibility for HF with reduced ejection fraction (HFrEF) trials were compared between the ASIAN-HF and BIOSTAT-CHF registries.

Results

One hundred and sixty-three HFrEF trials were identified. LVEF aside, the most frequently used inclusion criteria were NYHA functional class (69%), worsening HF and natriuretic peptides whereas the most common comorbidity-based exclusion criteria were acute coronary syndrome (64%) and valvular heart disease (47%). On average, 20% of registry patients were eligible for enrolment. Eligibility distributions did not differ between Asian (N=4868) and European (N=2545) registry populations. With time, HFrEF trials became more restrictive, with a change in eligibility from 0.4 in 1985-2005 to 0.19 in 2017-2021. When frequency in trials is taken in consideration, prior MI, NYHA functional class, age and prior HF hospitalization had the highest impact on restrictiveness.

Conclusion

Based on data for 14 eligibility criteria, one-fifth of registry patients were eligible for phase 3 HF trials and eligibilities were comparable between Asian and European registry patients.

INTRODUCTION

Eligibility criteria of phase III randomized controlled trials in heart failure (HF) defines a target population in which an intervention is most likely to be efficacious.[1,2] However, restrictive eligibility criteria has been a long-standing concern as it can jeopardize trial accrual and lead to overly narrow trial populations.[3] In the latter, 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, it is patients with more complex disease that would benefit most from treatment.

HF trials have become larger and take longer to complete as a series of successful drug therapies translated to an initial decline in mortality.[4] Although this decline in mortality have since plateaued[5,6], proving incremental benefit of new therapy amid existing background treatment becomes more challenging. In efforts to enrich for outcome event rates, inclusion and/or exclusion criteria can become more complex and restrictive.[7] Overly complex criteria increase the risk for low enrolment, protocol amendments or in worst cases, non-completion. Of 644 HF trials in ClinicalTrials.gov from 2005 to 2015, more than half of study terminations were due to poor accrual.[8] Similarly, A gradual decline in completed HF trials was observed as industry and researchers divert resources to other clinical domains.[9] Decisions on inclusion and exclusion criteria of a trial clearly affects its length and cost.[3] It is thus time to move from carry-forward criteria selection to one that is data-guided.[10] This approach decreases reliance on assumed recruitment rates, thereby minimising opportunity costs lost from protocol amendment or study extension.

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.[11] With larger geographical differences also comes greater heterogeneity in patient characteristics and outcomes of these 'megatrials'.[4] In the EVEREST trial for hospitalized heart failure, regional differences were evident for patient co-morbidities, biomarkers, treatment and outcomes.[12] 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 and generalizability as well as improve trial efficiency. In this study we aim to assess and compare the influence of most commonly used eligibility criteria for trials in heart failure 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 gradual addition common inclusion and exclusion criteria on overall trial eligibility.

METHODS

Selection of heart failure trials

Clinical study registration as of 31 December 2021 was downloaded from Aggregate Analysis of ClinicalTrials.gov[13], a daily updated trial registration database.[14] Relevant studies were identified by the 'condition or disease' of heart failure and its equivalent terms (Supplementary table 1). We characterized all interventional studies for HF and then, focused analysis on eligibility criteria for phase 3 trials for HF with reduced ejection fraction (HFrEF). HFrEF trials were defined as those which included patients with left ventricular ejection fraction (LVEF) of an upper limit of 40% and below.

The primary outcome variable is trial eligibility criteria. This information is entered by investigators as free text; therefore, it first needs to undergo text analysis into a structured data format. Other trial-related variables were available in structured formats and analysed as potential predictors of trial eligibility. These are study start year, anticipated sample size and intervention type. In addition, we defined a study's primary funder by the following definition: industry-funded if its lead or collaborator is industry, NIH/ other government agency if present as lead or collaborator for a non-industry sponsored study, and otherwise it is a healthcare or academic institution or other.

Text analysis of trial eligibility criteria

For text analysis, we used combined two methods to capture all relevant clinical entities in the eligibility criteria. First, we trained a machine-learning (ML) algorithm to recognize named-entities using a sample of manually annotated criteria combined with a standardized dictionary from the Unified Medical Language System.[15] Second, we identified remaining unmarked entities using scripts defined by Apache

Unstructured Information Management Architecture Ruta Rules[16]. Both steps were implemented within a natural language processing (NLP) tool known as CLAMP (Clinical Language Annotation, Modelling, and Processing).[17]

During manual annotation, we randomly sampled ten percent (n=37) of the phase III trials and annotated the clinical entities within the eligibility criteria. Relationships between interdependent entities such as a laboratory measurement and its value were also specified. We developed a first version of an annotation guide based on categories consistent with the Observational Health Data Sciences and Informatics Common Data Model health data standards.[18] These categories were condition (includes diagnosis and medical history), measurement (numerical or categorical) and their corresponding values and units, demographic characteristic or drug. Information that are not present in routine medical records, for example, ability to comply with follow-up, are excluded from analysis.

Manual text annotation was done within LANN, a team-based annotation tool that is compatible with CLAMP.[19] We compared annotations between the two annotators (YMFL and WJW) and revised the guidelines iteratively. A set of gold standard criteria were determined based on the final agreement between annotators. Overall inter-annotator agreement was 0.615 for Cohen's Kappa and 0.841 for F1 performance measure, an average of precision and recall which ranges between 0 and 1.[20] The finalized annotations were used as input data for a ML model training using five-fold cross validation and conditional random fields algorithm from the CRFSuite library. F1 scores for condition, measurement, measurement value, demographics and drugs were 0.581, 0.646, 0.719, 0.364 and 0.448, respectively. Cross-checking with the original text was done up to a point where every relevant entity was extracted (in 40% of trials).

The final structured clinical entities were then exported as individual text files for analysis in R. In calculating trial eligibility, binary criterion such as presence of comorbidities can be applied as an inclusion or exclusion criterion whereas continuous variables, i.e., laboratory, ECG, physical examination measurements were specified as ranges with minimum and maximum thresholds. Arbitrary limits of minimum of 0 and maximum of 2000 were used where upper and lower limits were not explicitly specified.[21]

Data sources for target population

A target population or domain refers to all patients to whom trial findings can be applied whereas a trial population is a smaller 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 Asian heart failure registry (ASIAN-HF).[22,23] The former consists European HF patients while the latter enrolled patients from 10 Asian countries. Both HF registries included physician-diagnosed HF patients with a majority of patients having HFrEF. Only patients with LVEF less than 40% were included from the BIOSTAT cohort to maintain comparability with ASIAN-HF.

Registry variables were screened and the following common variables across registries were used for the estimation of eligibility scores: age, anaemia, atrial fibrillation (AF), body mass index (BMI), cancer, chronic kidney disease, 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, serum potassium, QRS duration, revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), stroke, sinus rhythm, use of ACE-inhibitors or angiotensin-2 receptor blockers (ARB), beta-blockers (BB), mineralocorticoid receptor antagonist (MRA), history of worsening heart failure (HF hospitalization in past 6 months for ASIAN-HF or 12 months in 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 study trait, GIST 2.0 introduced by Sen et al.[21,24] The score represents an estimated proportion of the target population that is trial-eligible and have values between 0 and 1. This representativeness score is first calculated by treating each criterion independently, be it the presence or absence of patient characteristic(s) or fulfilment of defined thresholds in numeric measurements such as laboratory tests. Then, an overall weighted representativeness score is estimated based on the proportion of registry patients who fulfil all criteria. The estimation method standardises numeric data and accounts for interdependence across criteria in each

trial. Patient weights were also applied and these were calculated as a residual difference from a non-linear Gaussian kernel-based hypersurface plane. To determine the criterion most likely to impact eligibility, eligibility scores were inversely weighted by the frequency of occurrence in trials where the lowest weighted scores would be seen in the most restrictive criteria.

Missing data in the registries ranged from 1% to 54% and were multiply imputed by chained equations.[25] The number of imputations was set at 10.[26] Statistical analysis was performed using R statistical software 4.1.2 (R Core Team, 2021), STATA SE 15 (StataCorp LP, College Station, Tx) and MATLAB R2021a. Statistical significance was set at 0.05.

Eligibility in theoretical trials

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

RESULTS

Characteristics of heart failure phase III trials

As of end December 2021, 4425 studies for heart failure were identified on ClinicalTrials.gov and 375 were phase III HF trials. Of these, 163 (44%) were HFrEF trials, 9% were 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 whereby more than half (55%) were initiated within the recent 10 years. 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 overall median trial size of 170

patients. Drugs were the most commonly investigated intervention, accounting for 68% of phase III trials. By primary source of funding, half (51%) were industry-funded.

Inclusion and exclusion criteria applied in HFrEF 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 heart failure (23%) and natriuretic peptide level (20%). A range of patient medical history 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%), stroke (33%), respiratory disease (28%) and cancer (25%). Measures of organ dysfunction and performance status often used were renal function (55%), hepatic function (21%) and anaemia (anaemia status or hemoglobin cut-off) (17%).

Also gaining importance are concomitant background treatment. Half (48%) required participants to be on standard of care medical and/or device therapies, in which a quarter specified ACEI /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 were specified in two percent of HFrEF trials, largely as 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 registry were included for analysis. Baseline characteristics are presented in Supplementary table 2. Compared to 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 lower prevalence of prior HF hospitalization (30% in 12 months vs 39% in 6 months). Rate of comorbidities were generally higher in European patients most notably ischaemic heart disease (68% vs 52%), AF (43% vs 18%) and COPD (17% vs 8%) with the exception of chronic renal disease (31% vs 47%). Use of HF medications between populations were similar for ACEI/ARB, BB and MRA. Almost all of the European registry patients were on

diuretics (99.5% vs 82%) as this was a requirement for participation in the BIOSTAT-CHF cohort.

Between one and fourteen eligibility criteria were applied in the estimation of eligibility. Summarising across 163 HFrEF trials, about one-fifth of the combined target population were eligible (median eligibility score 0.19 (95% CI 0.14, 0.24)). Figure 2 shows that the distribution of eligibility scores across trials were broadly similar between Asian and European populations. Median eligibility was marginally higher in the Asian patients (0.20 vs 0.17) but was not statistically significant (p=0.3).

Table 3 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 seven years show a reversal, increasing to median eligibility of 0.19 (p-value=0.02). By intervention type, drug trials enrolled a more representative pool of participants (median score 0.24) compared to device and procedural or diagnostic trials (median were both 0.09, p<0.001). Further, trial eligibility differed by primary funding source; eligibility was highest among academic /healthcare institution-funded trials, followed by those funded by NIH and lastly, industry-sponsored trials. The anticipated size of trials, however, was not predictive of eligibility (p=0.4).

Comparing impact of individual criterion by target population

Trial eligibility can be limited when one or more exceptionally restrictive criterion is present. Of the criteria assessed, prior HF hospitalization, MRA background treatment and anemia were most restrictive with eligibility scores of 0.38, 0.56 and 0.61 respectively (Figure 3). Eligibility based on single criterion were 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 to Asian patients. On the other hand, for trials which focus 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. (Supplementary figure 1) LVEF was not compared because it is present in 100% of trials.

Eligibility using multiple criteria in theoretical trial design

For a theoretical design, the strongest determinants of eligibility were background therapy of ACEI/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 to IV (Figure 4A). Factoring a further exclusion of patients with implanted devices, COPD, cancer, stroke, estimated GFR ≤ 30 ml/min/1.73m2, hemoglobin <10g/dL and potassium ≥5.5mmol/L, leaves about one-fifth (18%) eligible. Eliminating NYHA class IV led to only 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 to LVEF ≤40% (Figures 4C and 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. (Supplementary figure 2). For a trial design which considers a triple HF background therapy (add-on MRA), overall eligibility was halved in comparison to a broader double therapy of ACEI/ARB+BB. (Supplementary figure 3).

Table 1. Heart failure phase III trial characteristics

	Outpatient						Hospitalized HF		Total	
	HFrEF		HFpEF		Any EF					
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%

Table 1 (continued). Heart failure phase III trial characteristics

	Outpatient						Hospitalized HF		Total	
	HFrEF		HFpEF		Any EF					
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%
Other[a]	6	3.7%	1	3.0%	5	4.4%	0	0%	12	3.2%

HFpEF trials were those which recruited only patients with LVEF more than or equal 40%, hospitalized HF trials evaluated therapies in acute decompensation or hospitalized patients and the remaining are categorised as non-LVEF selective trials

a Other includes managed care or non-profit organisations, individual investigators and networks.

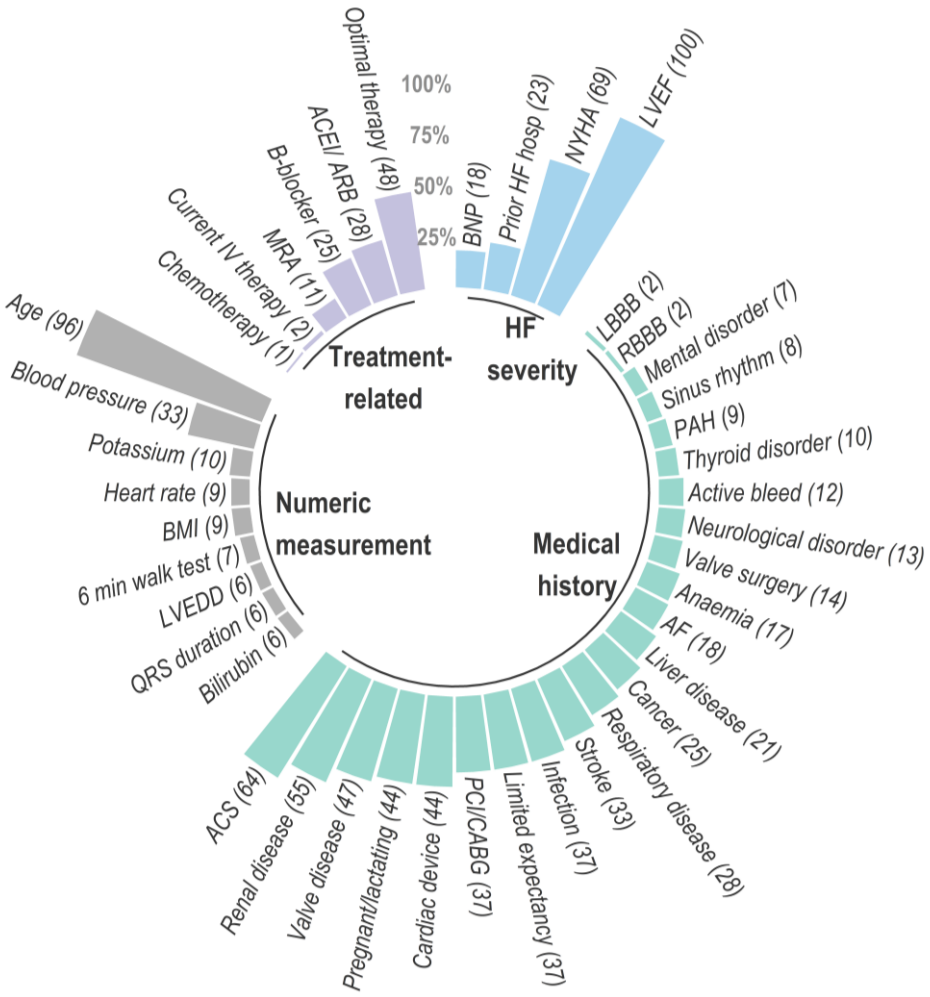


Figure 1. Ranked eligibility criteria in HFrEF trials (n=163). Value in bracket indicate percentage. Anaemia consists of iron-deficiency anaemia and haemoglobin and ferritin thresholds. Renal disease consists of serum creatinine, estimated glomerular filtration rate, chronic or end-stage renal disease.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

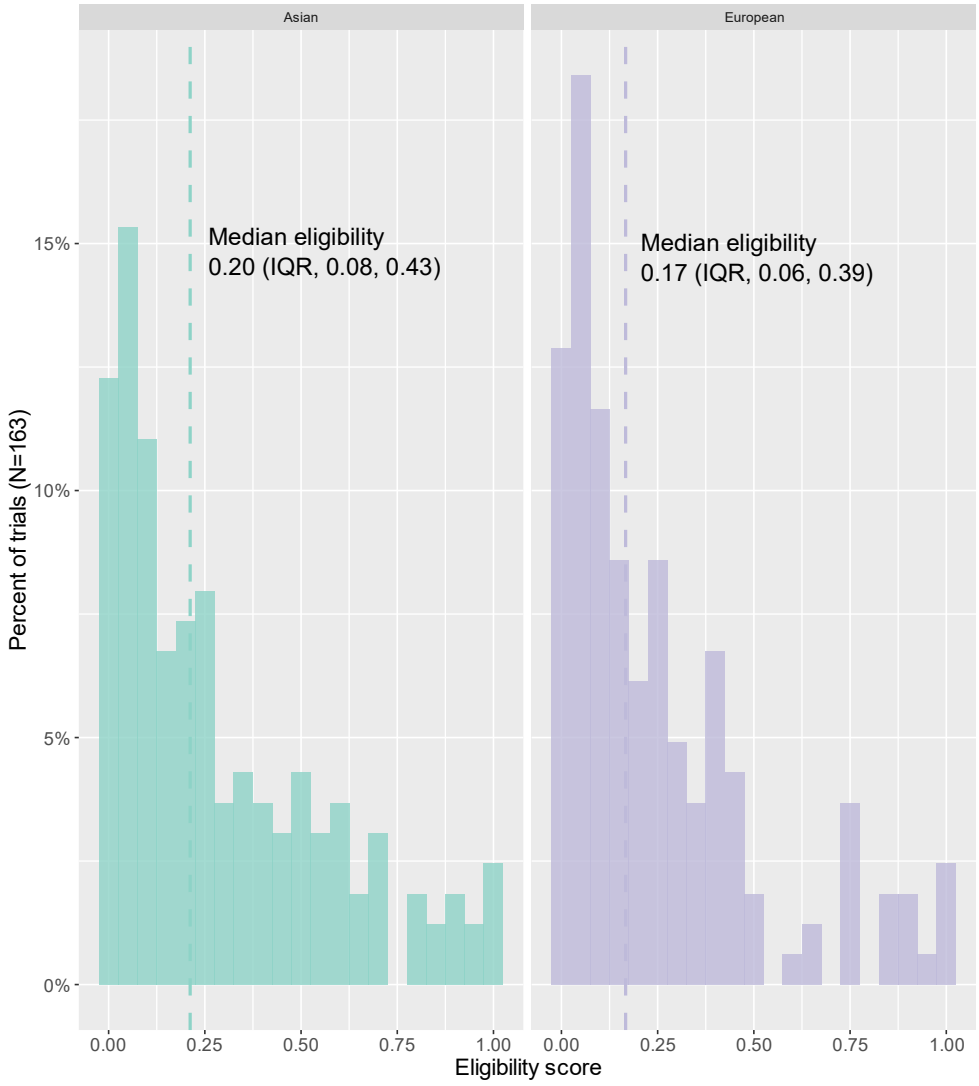


Figure 2. Distribution of eligibility scores for HFrEF trials by Asian and European target populations. Dashed lines indicate median score. p-value= 0.18 for Wilcoxon rank sum test between populations; IQR, interquartile range

Table 3. Median eligibility by 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	
Other[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, U.S. Department of Health and Human Services.
a, Kruskal Wallis rank sum test
b, Includes managed care or non-profit organizations, individual investigators and networks.

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

Figure 3. Ranked eligibility scores per criterion by target populations (from most to least restrictive). Value in brackets represent percentage of HFrEF trials (n=163).

a, typically exclusion criterion. ACEI, 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; Hb, hemoglobin; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention;

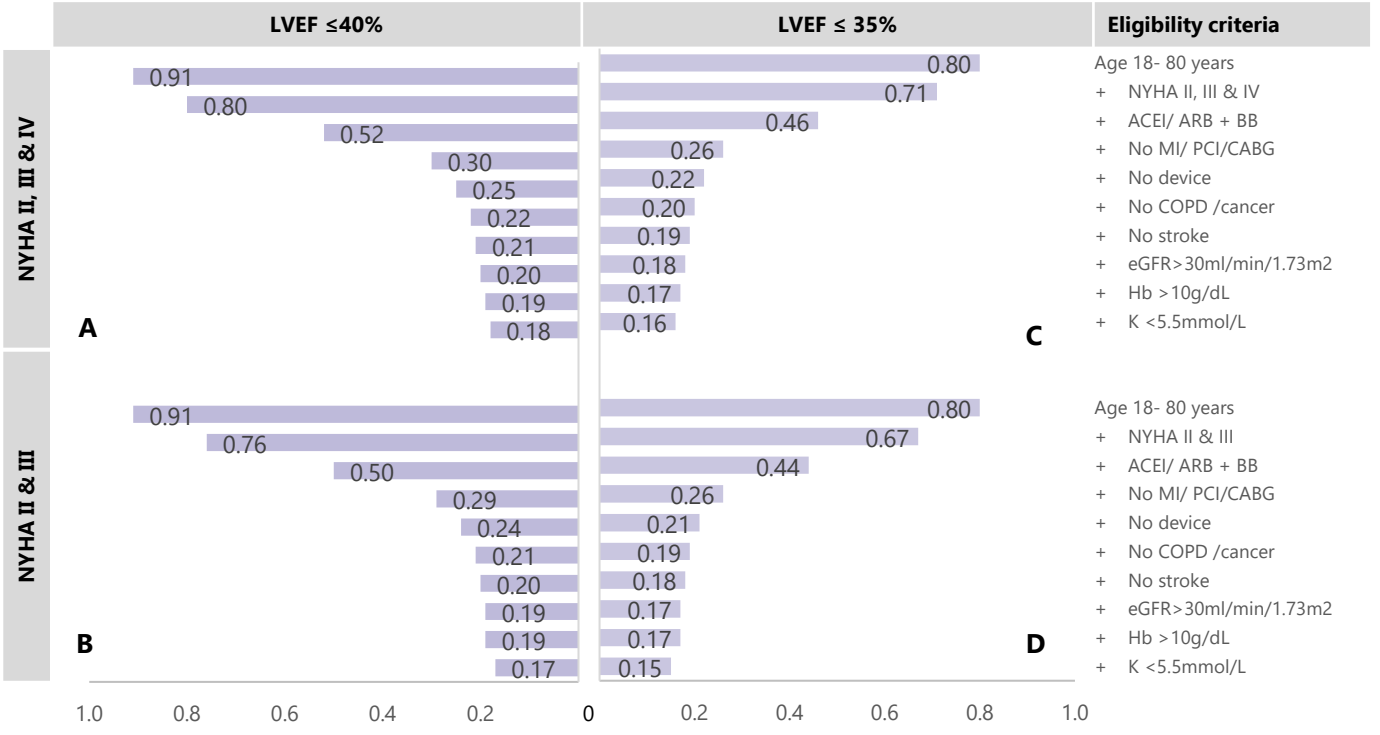


Figure 4. Cumulative eligibility for theoretical heart failure trials per addition of eligibility criteria stratifying by (A) LVEF < 40% & NYHA II, III & IV; (B) LVEF <40% & NYHA II & III; (C) LVEF ≤35% & NYHA II, III & IV; (B) LVEF ≤35% & NYHA II & III.

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 heart failure severity, namely LVEF, NYHA class, prior worsening of HF, natriuretic peptides followed by cardiovascular comorbidities and events/ procedures i.e., history of MI, cardiac devices, revascularization and optimised background HF treatment. Second, eligibility of two distinct HF patient populations for existing HFrEF trials did not significantly differ; they were both low in that only 20% on average were eligible. Accordingly, we identified the most restrictive criteria amongst these trials and these were prior HF hospitalization, MRA background treatment and anemia. When frequency in trials is taken in 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 trial eligibilities and showed we can test assumptions on 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 to European patients, although most clinical trials are designed and weighted towards Western Europe and North American populations.[27,28] 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 cost.[29] On this note, incorporating global sites for instance in Asia at the planning stage is cost-efficient given its high disease burden.[29]

With regard to 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 to eligibility estimates of single contemporary HFrEF drug trials, which ranged between 11- 35%.[30–32] Although estimates found for HFrEF trials are higher than the other large scale eligibility criteria analysis of cancer (2-5%) and diabetes trials (5%), there remains much room for improvement.[3,21]

Variation in eligibility between trials could be explained in part by the trial intervention type. Those which evaluated drugs make up a majority of explanatory trials in HFrEF, and are as expected, more representative than device or procedure trials with 25% average eligibility. Trials for cardiac devices and procedures are understandably more restrictive as these target small subsets of patients with arrhythmia or conduction problems, advanced heart failure or require device optimization. Next, it is important to recognize that eligibility for HFrEF trials was declining since the early 2000s with a slight increase in more recent years as a consequence of improved trial registration with time[33] and growing lists of eligibility criteria, including those for prognostic enrichment.[7] Availability of numerous guideline-directed drug therapy (GDMT) have to an extent decreased mortality in HFrEF, making present day HF trials increasingly difficult, complex and costly to conduct.[12,34]

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 overall proportion of eligible patients. Conversely, adding 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.[32,35] Next, although excluding patients with recent cardiovascular instability can be explained from a safety perspective, it is harder to justify exclusion of patients with comorbidities such as iron-deficiency/ anaemia, COPD and cancer, which are all common in HF.[36,37] As these conditions tend to cluster with HF, whether from correlated risks or effects from chemotherapy, broadening of eligibility to include patients with these comorbid conditions would provide efficacy and safety data to a wider spectrum of patients.[1,38] 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.[39]

Considering difficulties in defining a single optimal GDMT, the Heart Failure Collaboratory agrees that a gradient of options for optimal treatment, from (i) no background therapy to (ii) any dose ACEI/ARB/angiotensin receptor-neprilysin inhibitor (ARNI) plus BB therapy and then (iii) add an MRA to finally a strictest requirement of (iv) 100% target doses of all GDMT, with sodium-glucose transporter-2 inhibitors could be considered.[40] In the present study, we assessed the impact of

including any dose background therapy of ACEI/ARB and BB and found between 10 and 30% absolute decrease in eligibility, which seems a fair trade-off particularly for evaluating 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 by guideline-directed medical therapy (GDMT) recommendations but on the actual use of these GDMTs. Instead of mandating specific drug classes, an alternative involves utilising a score to summarise type and intensity of background GDMT as basis to compare within and between trials.[40]

Among the strengths of this study is extensive analysis of eligibility criteria for trials from ClinicalTrials.gov, which is among the most complete trial register on drugs and devices by major pharmaceutical companies.[14] As therapeutics are eventually aimed at global markets, assessing eligibility using multinational registries from Asia and Europe enables testing the hypothesis for equal eligibility across patient profiles. There are also several limitations in this study. Information on 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 ASIAN-HF registry. That said, this diagnostic and prognostic criterion is infrequently measured in limited resource settings and selecting patients by natriuretic peptides is known to affect distribution of trial patient characteristics[2], raising further questions on generalizability. Next, eligibility criteria recorded in ClinicalTrials.gov represent only part of the full list, albeit the most important ones. 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 to actual eligibility. As the definitions for HF subtypes by LVEF evolves with time, HFmrEF subtype is more likely covered within the HFrEF trials with some minimal overlap with HFpEF trials.

It is necessary to acknowledge that both ASIAN-HF and BIOSTAT-CHF cohorts apply selection criteria and therefore have narrower spectrum of real-world patients than those found within electronic medical records (EMR). Nonetheless, present challenges such inherent lack of clarity in analogue clinical text, unstructured data formats and restriction to single centres or payer[41] 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 benefits of

rigorous data quality controls, completeness and patients that span multiple countries. 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 underestimation of eligibility by these features.

In the present study, we have shown value in characterizing eligibility in two distinct target populations. For instance, investigators for device trials who intend to select patients by history of implanted devices or QRS complex duration may need to be aware of lower eligible numbers in Asian sites whereas exclusion of patients with AF or history of MI will lead to comparatively slower accrual in European sites. Enrichment with criteria such as prior HF hospitalization potentially leads to higher enrolment rates in the Asian population, given that the proportion with prior hospitalization is already a-third higher in its a shorter observation period of 6 months. Understandably, these estimates can be sensitive to time and study site but here we demonstrate the feasibility of data-driven decisions at the design stage, which can potentially improve cost-efficiency of future trials. The use of observational patient data in guiding trial eligibility criteria is a fairly new concept. Several case studies have demonstrated promising opportunities in testing assumptions, simplify enrolment and expanding clinical trial access.[10] Further studies on impact of trial criteria decisions on cardiovascular event rates or hazard can be useful especially at pre-trial design stages. Existing obstacles related to unstructured data formats, data sharing policies and data quality can be overcome to enable real-time understanding of varying eligibility criteria decisions on patient eligibility and outcome event rates for trials.

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. By individual criterion, previous HF hospitalization, requirement of MRA therapy, and anaemia were most restrictive and could adversely impact accrual and generalizability of individual trials. On a broad perspective for HFrEF therapeutics, criteria that had most impact by both patient selectivity and frequency in trials were prior MI, NYHA class, age and previous HF hospitalization.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. And equivalent terms

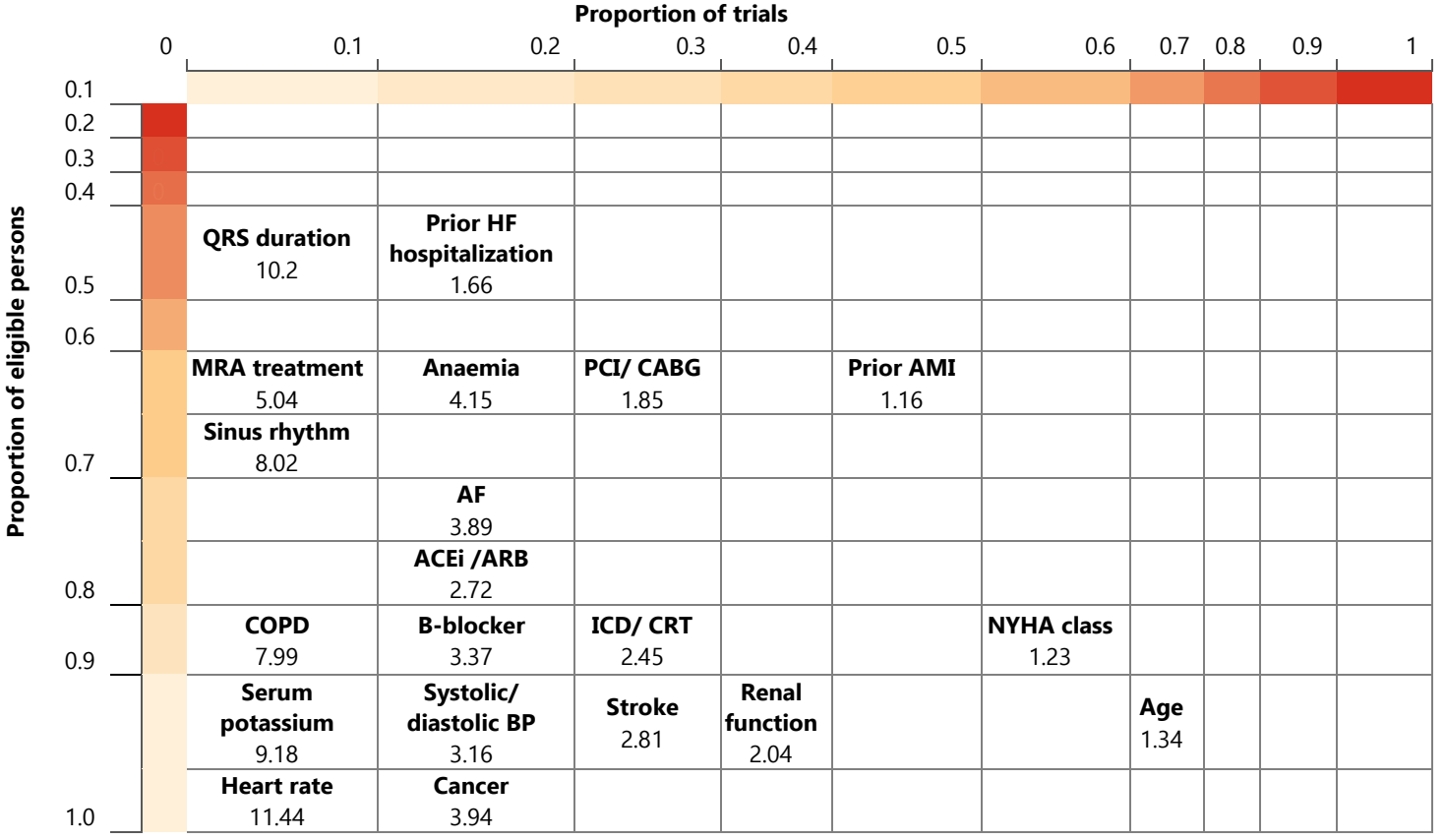
	Equivalent terms
Heart failure	Heart failure, myocardial failure, cardiac failure, ventricular failure, heart decompensation, myocardial decompensation, cardiac decompensation, ventricular decompensation, CHF, HFrEF, HFpEF, HFmrEF

Supplementary Table 2. Patient characteristics for BIOSTAT-CHF and ASIAN-HF registries

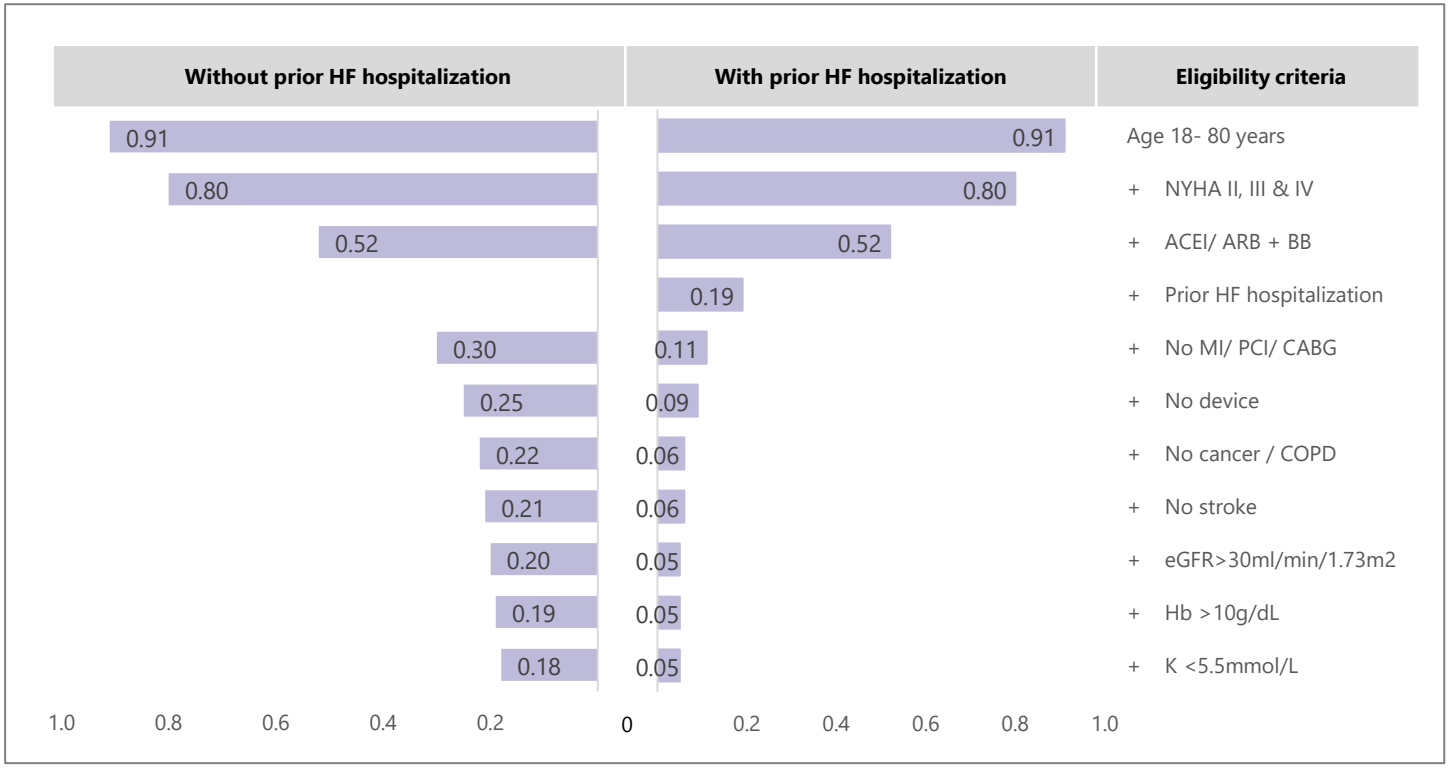
Patient characteristic	**BIOSTAT-CHF (n=2545)**		**ASIAN-HF (n=4868)**	
	n	**(%)**	**n**	**(%)**
Age(years)				
Mean (SD)	68.7	11.8	60.4	12.9
Median (IQR)	70	61.1, 77.5	61	52, 69
Men	2991	70.3	3799	78.0
BMI (kg/m^2)				
Median (IQR)	27.1	24.1, 30.6	24.2	21.7, 27.5
NYHA class				
I	166	7.1	621	14.1
II	1189	50.9	2459	55.7
III	842	36.1	1155	26.1
IV	138	5.9	183	4.1
LVEF (%)				
Mean (SD)	28.1	7.12	27.1	7.1
Median (IQR)	30	24.0, 35.0	27.4	21.9, 33.0
Clinical parameters, *median (IQR)*				
Systolic blood pressure (mmHg)	120	110,135	117	105, 130
Diastolic blood pressure (mmHg)	71	65.0,80.0	70	63, 80
Heart rate (bpm)	75	65.0,88.0	78	69, 88
Sinus rhythm	1404	55.2	3260	70.4
Heart failure history				
Prior HF hospitalization				
in past year	1254	29.5		
In past 6 months			1611	38.8
Ischaemic heart disease	2486	67.8	2507	51.5
Medical history				
AF	1085	42.6	858	17.6
MI	1110	43.6	1444	29.7

Supplementary Table 2 (continued). Patient characteristics for BIOSTAT-CHF and ASIAN-HF registries

Patient characteristic	BIOSTAT-CHF (n=2545)		ASIAN-HF (n=4868)	
	n	**(%)**	**n**	**(%)**
CABG	441	17.3	579	11.9
PCI	539	21.2	963	19.8
Cancer	86	3.4	160	3.3
Chronic renal disease	783	30.8	1821	46.6
COPD	427	16.8	383	7.9
ICD	222	8.7	250	5.1
Pacemaker	152	6.0	71	1.5
CRT-P/CRT-D	237	9.3	351	7.2
Stroke	275	10.8	335	6.9
Laboratory parameters, *median (IQR)*				
Creatinine (micromol/L)	101	83.0, 127	98	80, 133
eGFR (CKD-EPI formula, ml/min/1.73m^2)	60.8	45.2, 78.6	62.5	44.3, 81.8
Haemoglobin (g/dL)	13.5	12.1, 14.7	13.0	11.6, 14.5
Potassium (mmol/L)	4.3	4.00, 4.60	4.2	3.9, 4.6
Sodium (mmol/L)	140	137, 141	138	136, 141
Medication				
ACEI/ARB	1895	74.5	3752	78.0
B-blocker	2108	82.8	3788	78.8
Mineralocorticoid receptor antagonist	1325	52.1	2798	58.2
Diuretic	2532	99.5	3802	81.8



Supplementary figure 1. 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.



Supplementary figure 2. Cumulative eligibility for theoretical heart failure trials per addition of eligibility criteria with an enrichment criterion of prior HF hospitalization

Supplementary figure 3. 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)

3

Age, sex and racial/ ethnic representation in the design of trials for heart failure

Chapter 3.1

Sex Differences in the Generalizability of Randomized Clinical Trials in Heart Failure with Reduced Ejection Fraction

Megan Schroeder
Yvonne Mei Fong Lim
Gianluigi Savarese
Kiliana Suzart-Woischnik
Claire Baudier
Tomasz Dyszynski
Ilonca Vaartjes
Marinus JC Eijkemans
Alicia Uijl
Ronald Herrera
Eleni Vradi
Jasper J Brugts
Hans-Peter Brunner-La Rocca
Vanessa Blanc-Guillemaud
Sandra Waechter
Fabrice Couvelard
Benoit Tyl
Samuel Fatoba
Arno W Hoes
Lars H Lund
Christoph Gerlinger
Folkert W Asselbergs
Diederick E Grobbee
Maureen Cronin
Stefan Koudstaal

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ABSTRACT

Background

To understand how sex differences impact the generalizability of randomized controlled trials (RCTs) in patients with heart failure and reduced ejection fraction (HFrEF, we sought to compare clinical characteristics and clinical outcomes between RCTs and HF observational registries stratified by sex.

Methods and Results

Data from 2 HF registries and 5 HFrEF RCTs were used to create three subpopulations: one RCT population (n=16,917; 21.7% females), registry patients eligible for RCT inclusion (n=26,104; 31.8% females), and registry patients ineligible for RCT inclusion (n=20,910; 30.2% females). Clinical endpoints included all-cause mortality, CV mortality, and first HF hospitalization at one-year. Males and females were equally eligible for trial enrollment (56.9% of females and 55.1% of males in the registries). One-year mortality rates were 5.6%, 14.0%, and 28.6% for females and 6.9%, 10.7%, and 24.6% for males in the RCT, RCT-eligible, and RCT-ineligible groups. After adjusting for 11 HF prognostic variables, RCT females showed higher survival compared to RCT-eligible females (Standardized mortality ratio (SMR) 0.72; 95% CI 0.62 – 0.83), while RCT males showed higher adjusted mortality rates compared to RCT-eligible males (SMR 1.16; 95% CI 1.09-1.24). Similar results were also found for cardiovascular mortality (SMR 0.89; 95%CI 0.76-1.03 for females, SMR 1.43; 95%CI 1.33-1.53 for males).

Conclusion

Generalizability of HFrEF RCTs differed substantially between the sexes, with females having lower trial participation and female trial participants having lower mortality rates compared to similar females in the registries, while males had higher than expected cardiovascular mortality rates in RCTs compared to similar males in registries.

INTRODUCTION

There are sex and gender differences across multiple diseases and clinical syndromes. Some of the most profound differences can be seen in heart failure (HF).[1,2] Females and males differ in HF etiology, age, risk factors, biomarkers, pathophysiology, co-morbidities, and clinical presentation.[2–7] There is increasing awareness on sex differences in HF, however there are still large gaps in knowledge of sex-specific mechanisms, optimal treatment, and prognosis of HF.[2]

One driving factor of the knowledge gap in sex differences is the widespread underrepresentation of females recruited to HF clinical trials. From observational HF registries, the percentage of females with HF and reduced ejection fraction (HFrEF) in the population is around 30-50%,[8,9] whereas the percentage of enrolled females in HFrEF trials is on average 24%.[10] As a consequence, contemporary treatment guidelines are predominantly based on male-derived data.[10–13] Post-hoc analyses from trials and observational data currently suggest that females may need lower dosages.[14,15]

Currently, several uncertainties remain to be elucidated, for example i) differences in characteristics and background treatment are known to exist between trials and the broader population. Are these differences equal for males and females? ii) if differences in characteristics and treatment do vary by sex, to what extent are clinical outcomes influenced? Although there are now numerous calls to increase female representation in HF trials, especially from cardiology societies and regulators, little data is available to shed light on how under-enrollment of females in HFrEF trials affects generalizability to daily clinical practice.[16,17]

To address these uncertainties, in the present study, we sought to assess differences in clinical characteristics, medication dose and use, and explored unadjusted and case-mix adjusted mortality rates stratified for each of the sexes using individual patient data from 5 RCTs and 2 large HF registries.

METHODS

Data sources

Detailed information on the methods including data sources, endpoint definitions and collection codes can be found in a previous study.[18] Briefly, five HFrEF RCTs and two HF registries were included in this study. BEAUTIFUL and SHIFT were phase III ivabradine trials (n= 15732),[19,20] FAIR-HF and CONFIRM were phase III and phase IV studies on intravenous iron supplementation (n=763)[21,22] and PANTHEON was a phase II trial for neladenosone bialanate (n=427).[23] For final analysis, aggregated data from both treatment and placebo arms of each RCT were pooled to represent one RCT population (n = 16 917).

The Dutch CHECK-HF and SwedeHF registries enroll patients with clinician-judged HF and detailed information on the methods can be found elsewhere.[24,25] For the current analysis, only HFrEF patients, defined as those enrolled with left ventricular ejection fraction (LVEF) <40% were considered. To ensure consistency with CHECK-HF, only outpatients registered between 2000 to 2016 in SwedeHF (n=40 230) were included. Contrary to Dutch CHECK-HF, SwedeHF contains follow-up data, therefore any analysis of clinical outcomes was restricted to patients from SwedeHF. Ethics approvals were obtained by the original study investigators for the RCTs. CHECK-HF received approval for anonymized analysis of routine clinical data. In SwedeHF, patient consent to enrollment in the registry allows analysis of individual patient data.

Eligibility criteria, study population, and outcomes

The inclusion and exclusion criteria listed in the study protocols of the five RCTs were tabulated to identify common eligibility and ineligibility criteria (see Figure 1, Supplementary Table 1).[18] These common criteria were applied to the SwedeHF and CHECK-HF dataset to identify subgroups of patients who would have been eligible for trial participation or not. Data were then presented by the following groups and additionally stratified by sex: RCT, RCT-eligible, and RCT-ineligible (Figure 1). The following clinical outcomes at one-year were assessed: all-cause mortality, CV-mortality, and first HF hospitalization.

Statistical analysis

Continuous data are presented as mean with standard deviation while categorical variables were reported in absolute and relative frequencies. Mean and proportion differences between each group were calculated and reported as significant based on their corresponding 99% confidence intervals (CI). Unadjusted outcomes were calculated with cumulative incidence curves for each of the 6 subgroups outline above. The competing event for cardiovascular mortality was death from other causes whereas for first HF hospitalization, it was all-cause deaths. To test whether the RCT group was more, less, or equally likely to die than the RCT-eligible group, standardized mortality ratios (SMRs) were calculated and stratified by sex. SMRs were calculated by dividing the observed mortality count in the RCT group by expected mortality count in the RCT group. The observed mortality counts were the actual deaths recorded in the RCTs at one year. In standard SMR analysis, expected counts are the number of deaths that would be predicted if the study population (RCT group) were to have the same age and/or sex-specific rates as the standard population (RCT-eligible group).[26] However, one limitation in SMR analysis is the inability to account for case-mix between populations.[27]

To calculate more precise expected mortality counts in the RCTs, we used a validated prognostic model to apply characteristics of the RCT-eligible group to the RCT group.[28–30] We first fitted a Poisson model with 11 prognostic indicators from a validated MAGGIC HF risk score (age, sex, LVEF, NYHA class, serum creatinine, chronic obstructive pulmonary disease (COPD), diabetes, systolic blood pressure, body mass index (BMI), HF duration, smoking status) in a stepwise manner to the RCT-eligible SwedeHF group. Model 1 was the empty model, model 2 included age and sex, model 3 additionally included NYHA class, SBP, and creatinine, and model 4 was fully adjusted with all 11 prognostic variables. Each model with derived coefficients from the RCT-eligible population was then applied to each RCT to derive expected counts. If these prognostic factors and their associated risks were similar between the RCT and RCT-eligible group, then the expected deaths in the RCTs would be equal to the observed deaths leading to an SMR value of 1. Therefore, SMR ratios above 1 indicates that there are more observed deaths in the RCT population than would be expected based on characteristics derived from the RCT-eligible population, and vice versa for SMR ratios below 1.0. The SMRs for all trials were pooled using fixed effect meta-analysis and the corresponding 95% CI was determined using methods

described by Breslow and Day.[31] For first HF hospitalization, we did not estimate SMRs because existing prediction models for hospitalization are largely influenced by admission policies within individual health settings and hence have insufficient discriminative model performance.[32]

The largest RCTs (BEAUTIFUL and SHIFT) in this analysis only included patients who were in sinus rhythm (SR) and the BEAUTIFUL study included a population who had CAD; therefore, sensitivity analyses were conducted in subsets of registry patients who were (i) in SR or (ii) diagnosed with CAD. Missing data was multiply imputed by chained equations using the mice package in R. The number of imputations was set at 20.[33] Statistical significance was set at level 0.05. Statistical analysis was performed using the R statistical software version 3.6.1 (R Core Team, 2019) and Stata SE Version 15 (StataCorp LP, College Station, TX).[34,35]

RESULTS

Eligibility for potential trial enrollment

Out of 46 914 patients from the registries, 14 584 were females (31.1%). After applying the harmonized set of eligibility criteria, 8294 out of 14 584 (56.9%) females and 17 818 out of 32 330 (55.1%) males in the registries were considered eligible for RCT for a final RCT-eligible group of 26 104 (31.8% females). Cancer was the most restricting criteria with 27.4% of females and 28.1% of males excluded. ACEI and ARB use at baseline differed between sexes with 15.7% of females and 11.6% of males who were ineligible for not taking ACEI or ARBs (Supplementary Table 2). In the RCT population, the observed number of females was significantly lower with 3 663 out of 16 917 (21.7%) patients (Figure 1).

Baseline characteristics

Baseline characteristics for the RCT population, RCT-eligible and RCT-ineligible patients stratified by sex are shown in Table 1. Overall, patients in the RCTs were younger compared to RCT-eligible and RCT-ineligible patients, with similar directions for both females (66.3 vs 73.9 vs 76.7 years) and males (62.8 vs 69.8 vs 73.8 years) in the three groups respectively. Compared to males, females were significantly older in all three groups (Table 1). Similarly in females and males, a minority of the RCT population had a LVEF below 30% (28.7% and 32.6%) as opposed to both the registry

populations of RCT-eligible (47.0% and 56.1%) and RCT-ineligible patients (43.0% and 48.6%) for females and males respectively. Although females in all three groups had a higher LVEF compared to males, the proportion of patients in NYHA functional class III/IV was also highest in females compared to males in all groups (46.5% vs 36.4%; 48.1% vs 42.9%; 46.6% vs 42.6%; in the RCT, RCT-eligible and RCT-ineligible groups, respectively).

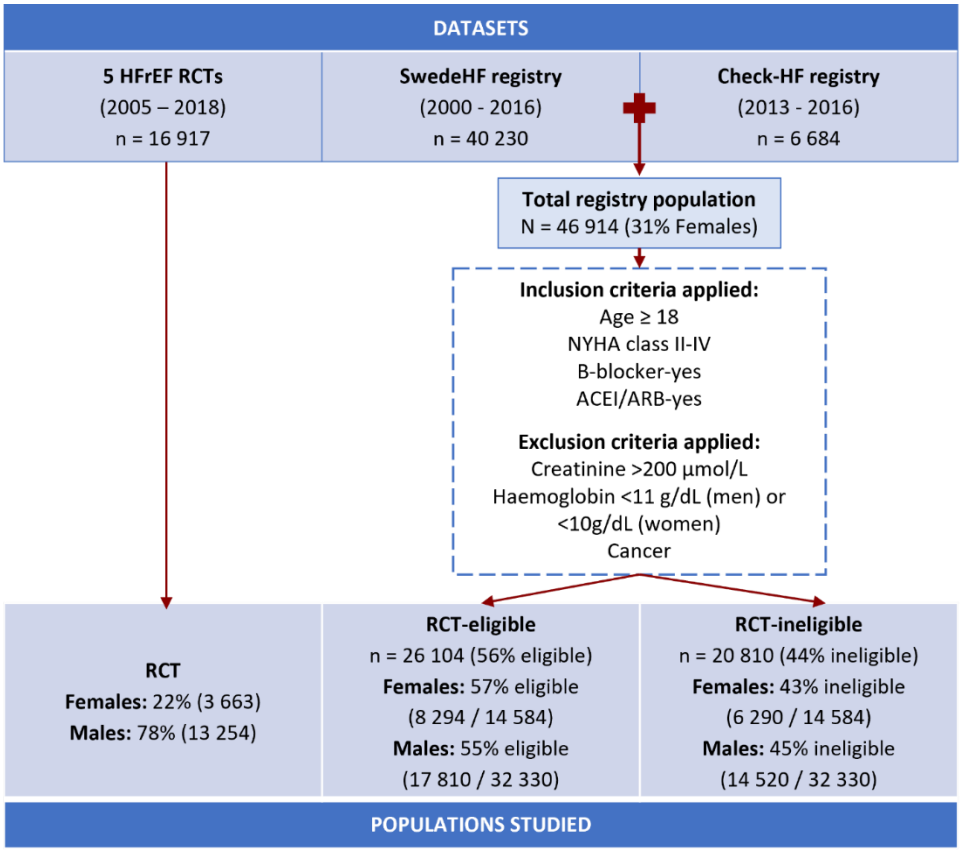


Figure 1. Flowchart of the selection of studied populations from available datasets and the respective proportion of males and females

Table 1. Baseline characteristics compared between RCT populations, RCT-eligible registry population, and RCT-ineligible registry population, stratified by sex.

	RCT			RCT-eligible registry			RCT-ineligible registry		
	Females	**Males**	**p-value[b]**	**Females**	**Males**	**p-value[b]**	**Females**	**Males**	**p-value[b]**
n	3 663	13 254		8294	17 810		6 290	14 520	
Demographics and lifestyle, mean (S) or %									
Age (years)	66.3 (9.9)	62.8 (9.9)	***	73.9 (9.1)	69.8 (12.2)	***	76.7 (9.7)	73.8 (9.3)	***
Smoking history			***			***			***
Never	72.4%	29.0%		53.0%[a]	35.50%[a]		57.0%	37.80%	
Previous/Current	27.6%	71.0%		47.0%[a]	64.50%[a]		43.0%	62.20%	
Clinical parameters, mean (SD) or %									
HF duration (months)	42.4 (58.4)	41.6 (58.7)		21.0 (58.6)	30.8 (58.8)	***	21.1 (32.2)	24.4 (31.2)	***
SBP (mmHg)	126.5 (14.9)	124.9 (14.9)	***	126.4 (16.0)	123.7 (20.5)	***	125.7 (17.1)	124.0 (15.2)	***
BMI (kg/m^2)	28.6 (5.5)	28.2 (4.6)	***	26.6 (6.5)	27.2 (6.0)	***	25.6 (4.7)	26.0 (4.3)	***
Creatinine (µmol/L)	90.3 (33.9)	101.6 (41.3)	***	90.6 (37.6)	103.4 (38.2)	***	108.9 (0.3)	129.7 (60.6)	***
LVEF (%)			***			***			***
0-29	28.7%	32.6%		47.0%	56.1%		43.0%	48.6%	
30-39	67.4%	66.6%		53.0%	43.9%		57.0%	51.4%	
40+	3.9%	0.8%		0.0%	0.0%		0.0%	0.0%	

Table 1 (continued). Baseline characteristics compared between RCT populations, RCT-eligible registry population, and RCT-ineligible registry population, stratified by sex.

	RCT			RCT-eligible registry			RCT-ineligible registry		
	Females	**Males**	**p-value[b]**	**Females**	**Males**	**p-value[b]**	**Females**	**Males**	**p-value[b]**
NYHA functional class			***			***			***
I	0.0%	0.1%		0.0%	0.0%		17.9%	22.9%	
II	53.5%	63.5%		51.9%	57.1%		35.4%	34.5%	
III	45.8%	35.7%		43.5%	39.4%		38.5%	36.2%	
IV	0.7%	0.7%		4.6%	3.5%		8.2%	6.4%	
NYHA functional class III/IV	46.5%	36.4%	***	48.1%	42.9%	***	46.6%	42.6%	***
Comorbidities %									
Hypertension	72.0%	67.0%	***	59.1%	54.7%	***	56.6%	54.7%	*
Diabetes mellitus	34.7%	33.5%		25.8%	27.8%	***	25.7%	27.8%	**
CAD	79.3%	87.8%	***	49.0% [a]	48.6%		48.1% [a]	57.4%	***
Valvular heart disease	14.9%	11.0%	***	24.2%	20.2%	***	26.5%	25.0%	*
Stroke or TIA	9.1%	9.3%		14.3% [a]	14.0% [a]		16.6% [a]	18.1% [a]	*
Atrial fibrillation/flutter	9.7%	8.9%		42.2%	46.7%	***	47.8%	54.9%	***
COPD	6.9%	9.3%	***	21.3%	18.6%	***	22.1%	20.9%	*

Table 1 (continued). Baseline characteristics compared between RCT populations, RCT-eligible registry population, and RCT-ineligible registry population, stratified by sex.

	RCT			RCT-eligible registry			RCT-ineligible registry		
	Females	**Males**	**p-value[b]**	**Females**	**Males**	**p-value[b]**	**Females**	**Males**	**p-value[b]**
Depression	4.6%	2.1%	***	6.2% [a]	4.3% [a]	***	6.5%	4.6%	***
Cancer	4.0%	2.4%	***	0.0% [c]	0.0% [c]	-	32.4%	32.2%	
Concomitant medications									
ACEI or ARB	90.2%	89.8%		100.0% [c]	100.0% [c]	-	63.7%	74.2%	***
Anticoagulant	2.8%	2.6%		40.7%	48.1%	***	33.4%	41.0%	***
Antiplatelet	74.7%	79.0%	***	48.2%	46.8%	*	45.5%	47.7%	**
MRA	47.1%	41.9%	***	38.4%	39.8%	*	33.9%	32.7%	
Betablocker	87.3%	87.5%		100.0%	100.0%	-	71.6%	75.0%	***
Digitalis glycoside	14.9%	14.7%		17.1%	17.0%		15.7%	13.9%	***
Diuretic	78.9%	69.6%	***	81.9%	78.1%	***	81.0%	77.7%	***

*p<0.05, **p<0.01, ***p<0.001

a. Data from SwedeHF only
b. Comparison between males and females (independent t-test for continuous and $\chi 2$ -test for categorical variables)
c. Statistical comparisons were not compared because they were part of the criteria for selecting RCT-eligible registry patients

Percentages may not add up to 100% due to rounding.

SBP, systolic blood pressure; BMI, body mass index; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; MRA, mineralocorticoid receptor antagonists; CI, confidence intervals

With regard to medical management of HF, the uptake of MRA was low for both sexes in all groups, (47.1% and 41.9% in the RCTs, 38.4% and 39.8% in the RCT-eligible, and 33.9% and 32.7% in RCT-ineligible, percentages for females and males, respectively). Overall, loop diuretics were prescribed more often in every female population compared to males, with highest difference in the RCT populations (78.9% in females vs 69.6% in males). Target dosing did not meaningfully differ between the sexes in any medication except for ACEI and ARB where less females received ≥50% - ≥100% of target dose for ACEI and ARB compared to males in the RCT-eligible (65.4% vs 71.6%) and RCT-ineligible groups (36.9% vs 46.4%), but not in the RCT group (54.7% vs. 56.8%) (Supplementary Table 3).

Unadjusted clinical outcomes

Cumulative incidence curves for unadjusted cumulative incidence rates for all-cause and cardiovascular mortality, and HF hospitalization rates are shown in Figure 2 and unadjusted rates are summarized in Table 2. Females showed a lower unadjusted one-year mortality rate in the RCT population compared to males (5.6% vs 6.9%, P<0.01), but higher unadjusted one-year mortality rates compared to males in both the RCT-eligible (14.0% vs 10.7%, p<0.0001) and RCT-ineligible groups (28.6% vs 24.6%, p<0.0001). Similar trends were also observed for cardiovascular mortality (see Table 2). Rate of first HF hospitalization was lowest in the RCTs for both females and males (8.4% and 7.8%, p>0.05), and highest in the registry groups, (RCT-eligible: 23.2% and 24.8%, p<0.01; RCT-ineligible: 23.7% and 25.3%, P<.05 for females and males respectively) (Figure 2 and Table 2).

Case-mix adjusted clinical outcomes

Unadjusted SMRs (empty model) showed that females had 55% fewer deaths in the RCT group than expected (SMR 0.45; 95% CI 0.39 to 0.52), while males had 46% fewer deaths in the RCT group (SMR 0.54; 95% CI 0.51 to 0.58). Model 2, which adjusted for age between the younger RCT patients (mean age 63.5 years) and RCT-eligible patients (mean age 71.one-years), showed that females still had 31% fewer observed deaths than expected (SMR 0.69; 95% CI 0.60 to 0.80), whereas in males there was 7% higher observed deaths in the trials than expected (SMR 1.07; 95% 1.00 to 1.15). For cardiovascular mortality, the difference after adjusting for age was more

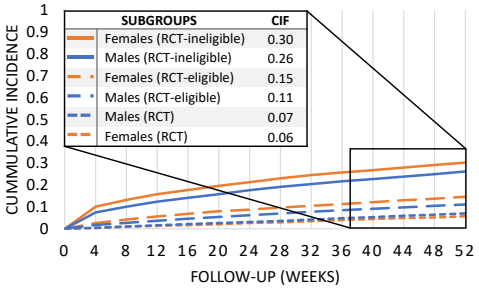
pronounced, with 12% fewer CV deaths in females, as opposed to a 31% increased number of observed CV deaths in male trial participants than expected (SMR 0.88; 95% 0.75 to 1.02 vs SMR 1.31; 95% CI 1.22 to 1.40, for females and males respectively). After full adjustment for all HF prognostic factors in model 4, these observed sex differences remained in place with 11% fewer CV deaths in females participating in trials than expected, compared to 43% more observed CV deaths in male trial participants than expected (SMR 0.89; 95CI 0.76 to 1.03 versus SMR 1.43; 95% CI 1.33 to 1.53) (Figure 3). The sensitivity analyses of SMRs calculated in subgroups of those only in sinus rhythm or those only with CAD did not meaningfully differ from the total population (Supplementary Figure 2 and Supplementary Figure 3).

Table 2. Unadjusted outcome rates between males and females, stratified by RCT population, RCT-eligible registry population, and RCT-ineligible population at one-year.

	RCT			RCT-eligible			RCT-ineligible		
	Females	Males	Proportion Difference (99%CI)	Females	Males	Proportion Difference (99%CI)	Females	Males	Proportion Difference (99%CI)
All-cause mortality	5.6% (201)	6.9% (910)	-1.4% (-2.5%, -0.3%) **	14.0% (1005)	10.7% (1671)	3.4% (2.1%, 4.6%) ***	28.6% (1468)	24.6% (3017)	4.0% (2.1%, 5.9%) ***
CV-cause mortality	5.0% (183)	6.2% (822)	-1.2% (-2.3%, -0.1%) **	10.6% (761)	8.1% (1267)	2.5% (1.5%, 3.6%) ***	20.2% (1038)	17.0% (2078)	3.3% (1.6%, 4.9%) ***
First HF Hospitalization	8.4% (308)	7.8% (1034)	0.6% (-0.7%, 1.9%)	23.2% (1660)	24.8% (3885)	-1.6% (-3.2%, 0.0%) **	23.7% (1214)	25.3% (3097)	-1.6% (-3.5%, 0.2%) *

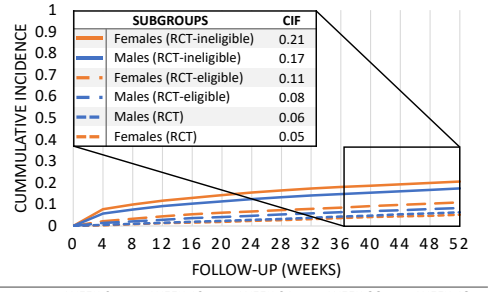
*p<0.05, **p<0.01, ***p<0.001 based on $\chi 2$ -test, 99% CI calculated

(A) ALL-CAUSE MORTALITY WITHIN ONE-YEAR



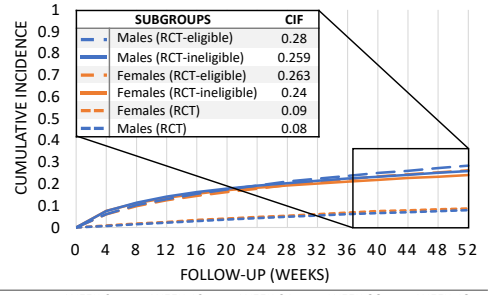
NUMBER AT RISK	WEEK 0	WEEK 12	WEEK 24	WEEK 36	WEEK 48
Females (RCT-ineligible)	5 133	4 245	3 924	3 629	3 396
Males (RCT-ineligible)	12 249	10 445	9 680	9 009	8 437
Females (RCT-eligible)	7 163	6 601	6 292	5 993	5 688
Males (RCT-eligible)	15 685	14 770	14 180	13 543	12 946
Males (RCT)	13 259	13 020	12 574	12 059	11 829
Females (RCT)	3 663	3 591	3 419	3 203	3 128

(B) CV-MORTALITY WITHIN ONE-YEAR



NUMBER AT RISK	WEEK 0	WEEK 12	WEEK 24	WEEK 36	WEEK 48
Females (RCT-ineligible)	5 133	4 231	3 907	3 621	3 388
Males (RCT-ineligible)	12 249	10 412	9 647	8 991	8 411
Females (RCT-eligible)	7 163	6 591	6 284	5 987	5 679
Males (RCT-eligible)	15 685	14 755	14 161	13 534	12 937
Males (RCT)	13 259	13 018	12 572	12 059	11 829
Females (RCT)	3 663	3 589	3 355	3 203	3 128

(C) HF HOSPITALIZATION WITHIN ONE-YEAR



NUMBER AT RISK	WEEK 0	WEEK 12	WEEK 24	WEEK 36	WEEK 48
Females (RCT-ineligible)	5 133	4 245	3 924	3 629	3 396
Males (RCT-ineligible)	12 249	10 445	9 680	9 009	8 437
Females (RCT-eligible)	7 163	6 601	6 292	5 993	5 688
Males (RCT-eligible)	15 685	14 770	14 180	13 543	12 946
Females (RCT)	3 663	3 581	3 412	3 199	3 125
Males (RCT)	13 259	13 020	12 574	12 059	11 829

Figure 2. Cumulative incidence curves and unadjusted event rates within one-year of follow-up for (A) All-cause mortality, (B) CV-mortality, and (C) HF hospitalization.

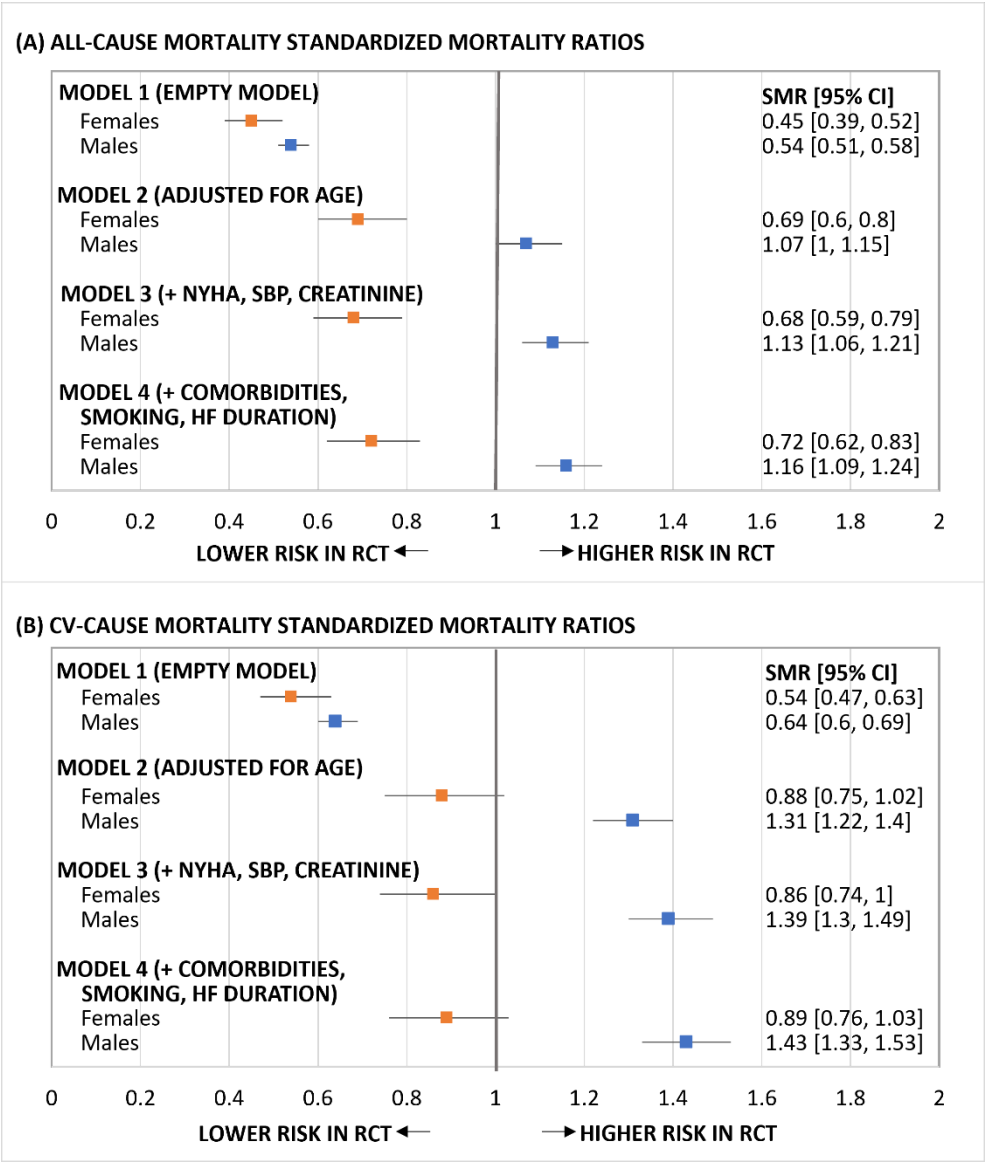


Figure 3. Standardized mortality ratios between RCT population and RCT-eligible population stratified by sex for (A) All-cause mortality and (B) CV-cause mortality.

DISCUSSION

Using individual patient data of over 62 000 patients from five HFrEF RCTs and two HF registries, we found several sex differences that impacted the efficacy of enrichment strategies in the clinical trials itself and influenced the generalizability of their results into daily clinical practice. 31% of patients in the registries were females, whereas 22% trial participants were females. Contrary to males, females in trials had a significantly better survival than expected from the registries, even after extensive adjustments for HF prognostic factors. HF hospitalizations were much more frequent in the observational registry compared to the trials, but here there was no relevant difference between the sexes. Taken together, these data show that although in- and exclusion criteria are similar, the populations of males and females enrolled in the RCTs show substantial differences in comparison with HF patients in the general population, and the magnitude and direction of these differences were unique to both sexes.

We confirm that there are sex-related differences in clinical profile, comorbidities, medication use, and outcomes in HFrEF.[2,36–38] Females in all 3 groups were older, less often smokers, had higher LVEF, less ischemic-related disease, more often diagnosed with hypertension, and had higher NYHA class III/IV proportions across all populations.[2,4,5,38–40] Females typically have shorter HF duration due to later onset HFrEF which was only confirmed here in the RCT population, but not in the registry populations.[8] Depression rates were more than doubled compared to males.[41] These sex differences were consistent across the 3 groups, however the proportion differences between the sexes were much more striking in the registry populations. Females and males in the RCTs were more similar. Target dosing did not meaningfully differ between the sexes in any group, which emphasizes the impact of male-derived treatment guidelines and the need for this topic to be explored further.

Data on prognostic differences between males and females with HFrEF are conflicting although females often seem to fare better than males.[4,7,8,42–44] In the present study, females in both registry populations, i.e., RCT-eligible and -ineligible, experienced higher unadjusted mortality rates due to all causes and CV causes compared to males in the registries, whereas the mortality rates were roughly similar between males and females in the trials. However, after adjusting for known prognostic factors in HF, males in the RCTs had consistently higher mortality risk in

comparison to males in the RCT-eligible population, with cardiovascular mortality risk 43% higher in the RCTs than expected in the registry. The higher percentage of CV death in the RCTs is consistent with use of enrichment strategies in inclusion/exclusion criteria. However, despite the same inclusion/exclusion criteria for males and females, females in trials showed no evidence of enrichment. On the contrary, there seemed a trend towards lower-than-expected CV mortality risk for females enrolled in trials compared to eligible females from the registries.

Enrichment strategies are often used in RCTs to identify patients who will experience CV events sooner than non-CV events in order to decrease time to target endpoint and improve efficiency of RCTs.[45] It is unclear what could explain this opposing response to enrichment. One explanation could be that there are some sex-specific factors affecting patient selection and willingness to participate. These are numerous reports that point out that females can be underrepresented due to significant patient-oriented biopsychosocial barriers which results in the exclusion of females who are elderly, obese, depressed, nonwhite, with greater comorbidity, and who have less social support.[7,36–38] This could hold true for the studied population here, as baseline characteristic differences between the RCT group and registry groups were larger for females than males. In addition, although females and males in the RCT were prescribed medication similarly, females in the registries were less often prescribed anticoagulants and ACEI or ARBs, which is consistent with previous literature.[2,4,15] This is concerning because the use of ACEI or ARBs was a significant driver for RCT-ineligibility in registry females and is possibly an additional barrier for female recruitment in RCTs. Patients in RCTs are also known to receive better care, and gender-related differences in clinical management has been shown to negatively affect females in the real world.[42,44] Taken together, these barriers could lead to a healthier female RCT population that is less representative of their real-world counterparts, especially in comparison to males.

Lastly, it is also conceivable that risk factors used to calculate the standardized mortality ratios have sex-specific impact. For example, diabetes, hypertension, and smoking have long been recognized as important risk factors in HF development, with evidence of a greater effect in females due to earlier onset adverse LV remodeling with increased wall thickness.[38,40,46,47] Although the MAGGIC risk model was chosen for this study due to its validity in predicting mortality for both sexes,[28,47] there are valid arguments for testing the interaction with sex in the

models or that sex disaggregation of results should be the norm in cardiovascular research.[48]

Study limitations

The strength of this study lies in large sample sizes and access to individual patient data from both trial and observational datasets. There are also potential limitations of the study. The harmonized criteria selected to define the RCT-eligible population were chosen based on data-availability and commonality between trials. Therefore, the percentage of patients eligible for trial inclusion is likely overestimated but allows for fairer comparisons between the RCT population and real-world. The RCTs involved in this study were selected based on the availability of data from industry partners. However, a comparison of baseline characteristics with contemporary trials does not show meaningful differences (Supplementary table 4). Combining RCTs can always present a source of heterogeneity in participant characteristics due to different investigational drugs being studied, trial phases and study countries. However, our sensitivity analyses in the CAD and SR subgroups support that exclusion criteria differences between the RCTs do not affect the main conclusion. Pooling of the placebo and treatment arms does not allow extrapolation of the mortality rates and risk from this study; however, pooling does not explain the sex differences seen in these results which was the main research question and conclusion of these results. Lastly, registries are regarded a fair representation of real-world patients with considerable depth of clinical data, although there can be some differences in characteristics and treatment practices between patients who were and were not enrolled in the registries. We also acknowledge that the trial and real-world populations differed on geographical location, healthcare systems and time of data collection.

CONCLUSION

Efficacy of enrichment in RCTs and the generalizability of RCTs towards the HFrEF population in the community differed substantially between the sexes, with females having lower trial participation and females who are enrolled in trials having lower than expected mortality rates compared to similar females in the registries, while males had higher than expected cardiovascular mortality rates in trials compared to similar males in registries. Failure to account for these differences or stratify future analyses by sex may influence appropriate translation of clinical trial results towards daily clinical practice or lead to under-powered RCTs because of ineffective enrichment.

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SUPPLEMENTARY MATERIAL

Supplementary table1. See Supplementary table 1 of Chapter 2.1

Supplementary table 2. Baseline characteristics of total registry population, RCT-eligible and RCT-ineligible stratified by sex

	Total Registries		**RCT-Eligible**		**RCT-non-eligible**	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
n	14 584	32 338	8 294	17 810	6 290	14 520
Demographics and lifestyle, mean (SD) or %						
Age (years)	75.1 (9.4)	71.6 (15.3)	73.9 (9.1)	69.8 (12.2)	76.7 (9.7)	73.8 (9.3)
Smoking history						
Never	54.7% (6727)	36.5% (10203)	53.0% (3793)	35.5% (5569)	57.2% (2934)	37.8% (4634)
Previous/Current	45.3% (5569)	63.5% (17731)	47.0% (3370)	64.5% (10116)	42.8% (2199)	62.2% (7615)
Clinical parameters, mean (SD) or %						
HF duration (months)	21.1 (47.3)	27.9 (66.6)	21.0 (58.6)	30.8 (58.8)	21.1 (32.2)	24.4 (31.2)
SBP (mmHg)	126.1 (16.5)	123.9 (25.5)	126.4 (16.0)	123.7 (20.5)	125.7 (17.1)	124.0 (15.2)
DBP (mmHg)	72.3 (11.8)	73.4 (15.8)	72.8 (12.9)	74.2 (12.3)	71.7 (10.6)	72.5 (9.9)
BMI (kg/m^2)	26.2 (5.7)	26.7 (7.4)	26.6 (6.5)	27.2 (6.0)	25.6 (4.7)	26.0 (4.3)
***Haemoglobin (g/dL)**	12.8 (1.2)	13.6 (2.5)	13.1 (1.1)	14.0 (2.1)	12.6 (1.3)	13.0 (1.5)
***Creatinine (µmol/L)**	98.5 (26.6)	115.2 (71.6)	90.6 (37.6)	103.4 (38.2)	108.9 (0.3)	129.7 (60.6)
LVEF (count, %)						
0-29	45.4% (6627)	52.8% (17060)	47.5% (3939)	56.1% (9997)	42.7% (2688)	48.6% (7063)
30-39	54.6% (7957)	47.2% (15270)	52.5% (4355)	43.9% (7813)	57.3% (3602)	51.4% (7457)

Supplementary table 2 (continued). Baseline characteristics of total registry population, RCT-eligible and RCT-ineligible stratified by sex

	Total Registries		RCT-Eligible		RCT-non-eligible	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
***NYHA functional class**						
I	7.7% (1128)	10.3% (3331)	0.0% (0)	0.0% (0)	17.9% (1128)	22.9% (3331)
II	44.8% (6536)	46.9% (15173)	51.9% (4308)	57.1% (10170)	35.4% (2228)	34.5% (5003)
III	41.3% (6026)	38.0% (12270)	43.5% (3605)	39.4% (7018)	38.5% (2421)	36.2% (5252)
IV	6.1% (894)	4.8% (1556)	4.6% (381)	3.5% (622)	8.2% (513)	6.4% (934)
Aetiology of HF						
Ischaemic heart disease	49.5% (7226)	47.8% (10233)	39.2% (3254)	44.7% (7962)	63.1% (3972)	42.3% (6149)
Non-ischaemic	50.5% (7358)	52.2% (11192)	60.8% (5040)	55.3% (9848)	36.9% (2318)	57.7% (8371)
***Serum creatinine (µmol/L) (count, %)**						
<90	55.8% (8135)	34.0% (10984)	58.7% (4867)	36.9% (6575)	52.0% (3268)	30.4% (4409)
90-109	17.9% (2608)	26.1% (8443)	18.7% (1555)	28.9% (5153)	16.7% (1053)	22.7% (3290)
110-129	10.5% (1533)	15.7% (5083)	10.4% (864)	16.4% (2925)	10.6% (669)	14.9% (2158)
130-149	6.0% (872)	9.2% (2975)	5.9% (491)	9.0% (1597)	6.1% (381)	9.5% (1378)
150-169	3.6% (521)	5.2% (1673)	3.2% (267)	4.5% (804)	4.0% (254)	6.0% (869)
170-209	3.3% (483)	4.9% (1583)	2.7% (227)	3.8% (678)	4.1% (256)	6.2% (905)
210-249	1.2% (173)	2.1% (677)	0.3% (23)	0.4% (78)	2.4% (150)	4.1% (599)
250+	1.8% (259)	2.8% (912)	0.0% (0)	0.0% (0)	4.1% (259)	6.3% (912)

Supplementary table 2 (continued). Baseline characteristics of total registry population, RCT-eligible and RCT-ineligible stratified by sex

	Total Registries		RCT-Eligible		RCT-non-eligible	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
***Haemoglobin (g/dL)**						
<8.0	0.1% (21)	0.1% (39)	0.0% (0)	0.0% (0)	0.3% (21)	0.3% (39)
8.0-10.9	12.0% (1754)	8.1% (2624)	7.5% (624)	0.0% (0)	18.0% (1130)	18.1% (2624)
11.0-12.9	40.8% (5949)	27.1% (8772)	41.0% (3400)	25.9% (4607)	40.5% (2549)	28.7% (4165)
13.0 - 14.9	37.8% (5507)	42.2% (13659)	41.0% (3401)	47.6% (8479)	33.5% (2106)	35.7% (5180)
15.0 - 16.9	8.7% (1268)	20.4% (6580)	9.8% (813)	24.1% (4301)	7.2% (455)	15.7% (2279)
17.0 and above	0.6% (85)	2.0% (656)	0.7% (56)	2.4% (423)	0.5% (29)	1.6% (233)
Comorbidities %						
Hypertension	58.0% (8465)	54.7% (17689)	59.1% (4904)	54.7% (9741)	56.6% (3561)	54.7% (7948)
Diabetes mellitus	25.7% (3755)	27.8% (8989)	25.8% (2137)	27.8% (4954)	25.7% (1618)	27.8% (4035)
Previous MI	29.7% (4328)	32.7% (10570)	30.0% (2489)	31.6% (5633)	29.2% (1839)	34.0% (4937)
CAD	48.6% (5981)	52.2% (15687)	49.0% (3513)	48.6% (8661)	48.1% (2468)	57.4% (7026)
Valvular heart disease	25.2% (3672)	22.3% (7222)	24.2% (2008)	20.2% (3599)	26.5% (1664)	25.0% (3623)
Stroke or TIA	15.2% (1874)	15.8% (4413)	14.3% (1021)	14.0% (2201)	16.6% (853)	18.1% (2212)
Atrial fibrillation/flutter	44.4% (5957)	50.1% (15047)	42.2% (3501)	46.7% (8318)	47.8% (2456)	54.9% (6729)
COPD	21.6% (3157)	19.6% (6344)	21.3% (1765)	18.6% (3313)	22.1% (1392)	20.9% (3031)
Depression	6.3% (777)	4.4% (1230)	6.2% (445)	4.3% (670)	6.5% (332)	4.6% (560)
***Cancer**	27.4% (2035)	28.1% (4681)	0.0% (0)	0.0% (0)	32.4% (2035)	32.2% (4681)

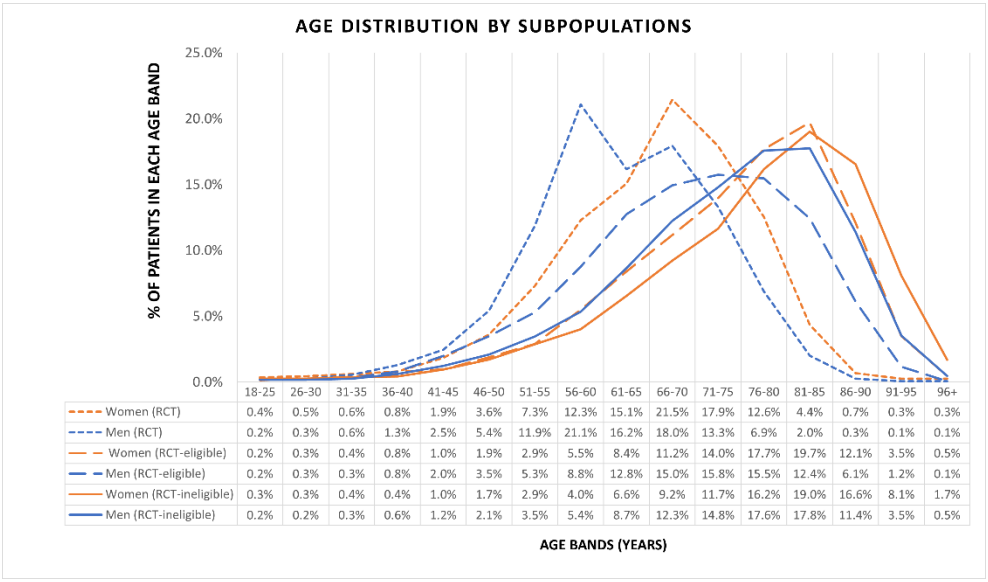
Supplementary table 2 (continued). Baseline characteristics of total registry population, RCT-eligible and RCT-ineligible stratified by sex

	Total Registries		RCT-Eligible		RCT-non-eligible	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
Medications						
***ACEI or ARB**	84.3% (12299)	88.4% (28578)	100.0% (8294)	100.0% (17810)	63.7% (4005)	74.2% (10768)
Antiplatelet	47.0% (6860)	47.2% (15256)	48.2% (3995)	46.8% (8334)	45.5% (2865)	47.7% (6922)
Anticoagulant	37.5% (5475)	44.9% (14518)	40.7% (3375)	48.1% (8572)	33.4% (2100)	41.0% (5946)
MRA	36.5% (5317)	36.6% (11836)	38.4% (3187)	39.8% (7087)	33.9% (2130)	32.7% (4749)
***Betablocker**	87.8% (12799)	88.8% (28697)	100.0% (8294)	100.0% (17810)	71.6% (4505)	75.0% (10887)
Digitalis glycoside	16.5% (2412)	15.6% (5037)	17.1% (1422)	17.0% (3025)	15.7% (990)	13.9% (2012)
Diuretic	81.5% (11884)	77.9% (25192)	81.9% (6792)	78.1% (13905)	81.0% (5092)	77.7% (11287)
Outcomes						
All-cause mortality	20.1% (2473)	14.0% (1005)	28.6% (1468)	16.8% (4688)	10.7% (1671)	24.6% (3017)
CV-cause mortality	14.6% (1799)	10.6% (761)	20.2% (1038)	12.0% (3345)	8.1% (1267)	17.0% (2078)
First HF Hospitalization	23.4% (2874)	23.2% (1660)	23.7% (1214)	25.0% (6982)	24.8% (3885)	25.3% (3097)

*Indicates an exclusion or inclusion criteria to determine RCT-eligible/ineligible population

Supplementary Table 3. Target doses of medication achieved between males and females, stratified by RCT population, RCT-eligible registry population, and RCT-ineligible population.

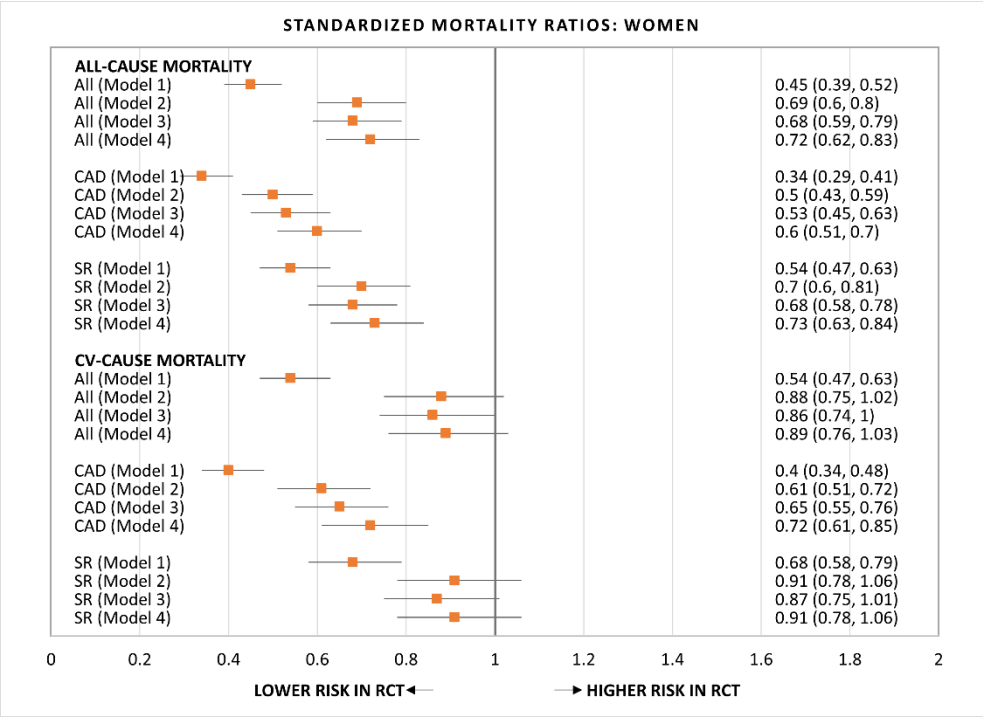
	RCT		RCT-eligible		RCT-ineligible	
	Females	Males	Females	Males	Females	Males
Medications (% of target dose)						
ACEI OR ARB						
0%	11.1%	10.5%	1.1%	0.8%	37.4%	26.8%
>0 - <25%	9.5%	8.4%	9.1%	7.2%	7.7%	8.2%
25- <50%	24.7%	24.3%	24.5%	20.4%	18.0%	18.6%
50- <100%	34.2%	36.0%	31.1%	30.3%	19.2%	21.9%
≥100%	20.5%	20.8%	34.2%	41.2%	17.7%	24.5%
MRA						
0%	60.5%	66.8%	61.6%	60.2%	66.1%	67.3%
>0 - <25%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
25- <50%	0.4%	0.2%	30.5%	32.9%	24.0%	24.8%
50- <100%	3.5%	3.7%	3.7%	3.5%	3.5%	3.6%
≥100%	35.6%	29.3%	4.1%	3.4%	6.4%	4.2%
Beta-blocker						
0%	12.7%	13.6%	0.1%	0.1%	28.5%	25.1%
>0 - <25%	16.4%	14.9%	10.2%	8.6%	9.6%	8.5%
25- <50%	28.2%	28.9%	28.4%	26.6%	22.4%	22.3%
50- <100%	27.1%	27.5%	35.6%	36.7%	24.7%	27.1%
≥100%	15.6%	15.1%	25.7%	28.0%	80.6%	17.1%
Medications (% of target dose)						
ACEI OR ARB						
0 - <50%	45.3%	43.2%	34.6%	28.4%	63.1%	53.6%
≥50% - ≥100%	54.7%	56.8%	65.4%	71.6%	36.9%	46.4%
MRA						
0 - <50%	60.9%	67.0%	92.1%	93.2%	90.2%	92.2%
≥50% - ≥100%	39.1%	33.0%	7.9%	6.8%	9.8%	7.8%
Beta-blocker						
0 - <50%	57.3%	57.4%	38.7%	35.3%	60.5%	55.9%
≥50% - ≥100%	42.7%	42.6%	61.3%	64.7%	105.3%	44.1%
All values are statistically significant P<.01 between males and females for the RCT, RCT-eligible, and RCT-ineligible populations						



	18-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80	81-85	86-90	91-95	96+
Women (RCT)	0.4%	0.5%	0.6%	0.8%	1.9%	3.6%	7.3%	12.3%	15.1%	21.5%	17.9%	12.6%	4.4%	0.7%	0.3%	0.3%
Men (RCT)	0.2%	0.3%	0.6%	1.3%	2.5%	5.4%	11.9%	21.1%	16.2%	18.0%	13.3%	6.9%	2.0%	0.3%	0.1%	0.1%
Women (RCT-eligible)	0.2%	0.3%	0.4%	0.8%	1.0%	1.9%	2.9%	5.5%	8.4%	11.2%	14.0%	17.7%	19.7%	12.1%	3.5%	0.5%
Men (RCT-eligible)	0.2%	0.3%	0.3%	0.8%	2.0%	3.5%	5.3%	8.8%	12.8%	15.0%	15.8%	15.5%	12.4%	6.1%	1.2%	0.1%
Women (RCT-ineligible)	0.3%	0.3%	0.4%	0.4%	1.0%	1.7%	2.9%	4.0%	6.6%	9.2%	11.7%	16.2%	19.0%	16.6%	8.1%	1.7%
Men (RCT-ineligible)	0.2%	0.2%	0.3%	0.6%	1.2%	2.1%	3.5%	5.4%	8.7%	12.3%	14.8%	17.6%	17.8%	11.4%	3.5%	0.5%

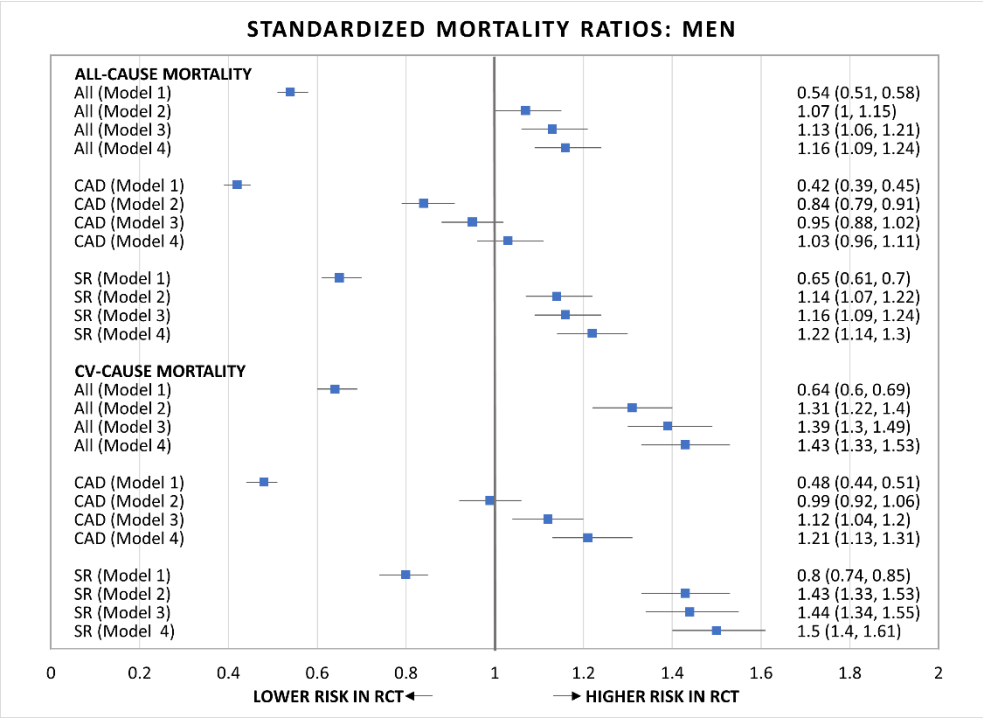
Supplementary figure 1. Age distribution by the following populations stratified by sex: RCT, RCT-eligible, RCT-ineligible.

Age distribution calculated by percentage of patients found in each age band. The oldest patients were the RCT-ineligible and RCT-eligible females, followed by the RCT-ineligible and RCT-eligible males. The RCT populations were younger, with males having the most patients in the younger age bands.



Supplementary figure 2. Sensitivity analysis for CV and all-cause SMRs for females in the total population, CAD subpopulation, and SR subpopulation.

Standardized mortality ratios for all-cause mortality and CV-cause mortality within one-year for females. SMRs calculated for females in the total population, those only in SR, and those only with CAD. HF prognostic factors from the MAGGIC risk model were added stepwise to each model until the fully adjusted model 4. The models were applied to the RCT-eligible population and the derived coefficients were then applied to the RCT population to predict expected deaths. SMRs were calculated by dividing observed RCT deaths by expected RCT deaths. Pooled SMRs estimated from five trials with their 95% CI were reported. Similar results were found in all populations, however the risk difference between the RCT and RCT-eligible population was even larger in the CAD subpopulation. Abbreviations as seen in Table 1.



Supplementary figure 3. CV and all-cause SMRs for males in the total population, CAD subpopulation, and SR subpopulation.

Standardized mortality ratios for all-cause mortality and CV-cause mortality within one-year for males. SMRs calculated for males in the total population, those only in SR, and those only with CAD. HF prognostic factors from the MAGGIC risk model were added stepwise to each model until the fully adjusted model 4. The models were applied to the RCT-eligible population and the derived coefficients were then applied to the RCT population to predict expected deaths. SMRs were calculated by dividing observed RCT deaths by expected RCT deaths. Pooled SMRs estimated from five trials with their 95% CI were reported. Similar results were found in all populations, however the risk difference between the RCT and RCT-eligible population were more similar in the CAD subpopulation. Abbreviations as seen in Table 1.

Supplementary Table 4. Baseline characteristics of contemporary HFrEF trials compared to RCT population in study.

	PARADIGM-HF	ATMOSPHERE	COMMANDER-HF	DAPA-HF	VICTORIA	EMPEROR-REDUCED	RCTs (combined)
	(N=8442)	(N=7063)	(N=5022)	(N=4744)	(N=5 050)	Treatment: 1863/Placebo: 1867	(n = 16 922)
Age (years)	64	63	66	66	67	67/66	64
Female sex – no. (%)	22	22	23	23	23	24/24	22
Clinical parameters, mean or %							
NYHA class, %							
I	5	2	3	0	0	-	0
II	70	69	44	68	59	75/75	61
III	24	28	49	32	40	24/24	38
IV	1	1	4	1	1	0/1	1
LVEF, %	29	28	34	31	29	27/27	31
NT-proBNP, pg.ml							
All	1615	1198	-	1437	3377	1887/1926	2036*
No AF/F	1444	1014	2850	1291	-	-	-
AF/F	1955	1652	-	1945	-	-	-
History of HF hospitalization, %	63	60	100[+]	47	84	31	-
Ischaemic aetiology, %	60	56	100	56	-	53/50	69
Blood pressure - mmHg							
Systolic	121	124	-	122	121	123/121	125
Diastolic	74	75	-	74	73	-	76

Supplementary Table 4 (continued). Baseline characteristics of contemporary HFrEF trials compared to RCT population in study.

	PARADIGM-HF	ATMOSPHERE	COMMANDER-HF	DAPA-HF	VICTORIA	EMPEROR-REDUCED	RCTs (combined)
	(N=8442)	(N=7063)	(N=5022)	(N=4744)	(N=5 050)	Treatment: 1863/Placebo: 1867	(n = 16 922)
Heart rate	72	72	-	72	73	71/72	74
eGFR	68	74	-	66	62	62/62	-
Creatinine	99	92	-	99	106*	-	99
Haemoglobin, g/L	140	138	-	136	134	-	140
Anaemia, %							
All	-	-	-	-	21	-	3
Males	21	22	-	28	-	-	3
Females	18	24	-	26	-	-	6
Smoking (current), %	-	-	-	14	-	-	16
Comorbidities (%)							
BMI, kg/m2	28	27	28	27	27*	28/28	28
Obese, %	32	27	29	35	-	-	32
Diabetes, %	34	28	41	42	47	50/50	34
Hypertension, %	71	62	75	74	79	72/72	68
MI, %	43	41	76	44	-	-	34
PCI, %	21	20	-	34	-	-	9
CABG, %	15	14	-	17	-	-	6
Stroke, %	9	7	9	10	12		9
Atrial fibrillation, %	37	34	0	40	45	36/38	32

Supplementary Table 4 (continued). Baseline characteristics of contemporary HFrEF trials compared to RCT population in study.

	PARADIGM-HF	ATMOSPHERE	COMMANDER-HF	DAPA-HF	VICTORIA	EMPEROR-REDUCED	RCTs (combined)
	(N=8442)	(N=7063)	(N=5022)	(N=4744)	(N=5 050)	Treatment: 1863/Placebo: 1867	(n = 16 922)
CAD, %	-	-	100	-	58	-	
COPD, %					17	-	
Concomitant medications (%)							
Diuretic	80	80	100	93	-	-	72
ACEi	78	100	72	56	-	-	
ARB	23	0	22	28	-	-	
ACEi or ARB	100	100	93	94*	74	-	90
B-blocker	93	92	92	96	93	95/95	88
MRA	60	37	77	71	70	70/73	
Digitalis glycoside	30	32	9	19	-	-	15
Ivabradine	2	1	-	5	-	-	-
CRT	7	6	2	7	-	12/12	-
ICD	15	15	9	26	28	31/32	-
*Limited data availability							

Chapter 3.2

Incidence of heart failure hospitalizations across ethnic groups in Malaysia: a population-based analysis from 2007 to 2016

Su Miin Ong
Yvonne Mei Fong Lim
Wen Yea Hwong
Stefan Koudstaal
Houng Bang Liew
Annamalar Muthu Muthuppalaniappan
Folkert W Asselbergs
Diederick E Grobbee
Ilonca Vaartjes
Sheamini Sivasampu

Submitted

ABSTRACT

Background

Almost no country-specific incidence trends data of de novo heart failure (HF) hospitalizations are available for Southeast Asia. This study aimed to determine the trends in incidence of HF hospitalizations and how these differ by age, sex and ethnicity in Malaysia.

Methods

Using a national hospital discharge database, we estimated and compared the rates of incident HF hospitalizations between 2007 and 2016 by direct standardisation. Quasi-Poisson models were used to estimate the incidence rate ratio (IRR).

Results

Of 105 399 patients who had incident hospitalizations for HF, 58 866 (55.9%) were men and 67 374 (63.9%) were 60 years and older. Majority (60.9%) were of Malay ethnicity. Women had lower incidence than men after adjusting for age, ethnicity and calendar year (IRR 0.77; 95% confidence interval 0.74-0.80). The absolute incident hospitalizations increased by 52.3%. In contrast, standardised incident HF hospitalizations decreased at an average of 1% per calendar year for both sexes. Age-standardised incidence was highest in the Indian ethnic group. However, this subgroup has also exhibited the highest annual rate of decline compared to other ethnic groups. Of note, Indian women had elevated risk of incident HF hospitalization compared to women of other ethnic groups.

Conclusion

Incidence of HF hospitalizations has decreased between 2007 and 2016 in Malaysia, irrespective of sex. However, absolute risks of HF hospitalizations remain higher in men and in the Indian ethnic group especially among Indian women. This represents opportunities for public health initiatives by targeting high-risk subgroups to reduce HF hospitalizations.

INTRODUCTION

Heart failure (HF) is a global public health problem with an estimated 26 million people in the world living with the condition.[1] Much of the epidemiologic data on HF come from western countries[2]. However, little reliable population-based data on the incidence of HF is available from this region to substantiate this claim.[3,4] Country-specific estimates for India and Japan have thus far relied on data extrapolations as representative data for the general population were not available.[3,5] While good quality clinical data on HF in the region is now available through the Asian Heart Failure registry, it may be less representative of general HF patients because like any HF registry, there were selection criteria. Patients were enrolled based on diagnosis of symptomatic HF and left ventricular dysfunction, and majority were treated at cardiology and HF specialty centres.[6] It has been shown that patients who were enrolled in a HF registry had different characteristics from those who were not, whereby enrolment was associated with better survival outcomes.[7]

Nationwide information on the incidence and time trends for HF is vital for evaluating changes in healthcare delivery and disease burden. Furthermore, determining the differences in incidence rates of HF by ethnic subgroups is necessary for understanding the burden of HF in this ethnically diverse region. Malaysia is a multi-ethnic country in Southeast Asia, where its population is made up of three major ethnic groups of Malays, Chinese and Indians as well as a smaller proportion of indigenous population and other ethnicities. This ethnic diversity allows the comparison of incidence of HF hospitalizations between groups of varying underlying cardiovascular risk profiles, lifestyle and dietary habits. Specifically, we aimed to determine the incidence for HF hospitalizations from January 2007 to December 2016 using population-based data in Malaysia.

METHODS

Study design and setting

This was a retrospective study using the national hospital discharge database. Data was extracted from the Hospital Discharge Registers for the period of January 2007 until December 2016. Inpatient admission records from public and private hospitals were compiled in centralised database known as the Patient Management

Information System (*Sistem Maklumat Rawatan Pesakit*) at the Health Informatics Centre, Ministry of Health (MOH) Malaysia. This initiative began with compilation of aggregated records from MOH hospitals since 1981. Then, individual patient data became available for MOH hospitals in 1999 while private hospitals started contributing data in 2008, followed by the public university and Ministry of Defence hospitals in 2017. It is worth noting that some data between 2012 and 2013 from several health centres were loss during a data migration process conducted by the data owner.

The Hospital Discharge Registers contain summary information about the patient admission episodes including admission and discharge date, and primary discharge diagnosis that was coded in International Classification of Disease-10 codes (ICD-10) in addition to demographic information such as age, sex and ethnicity. However, the information on patients' comorbidities and drug therapies were not available in the register.

Malaysia is an upper-middle income country of population size of 31.7 million in 2016, with a multi-ethnic population distribution as follows: 68.6% *Bumiputera* (comprising mainly of Malay ethnicity), 23.4% Chinese, 7.0% Indians and 1.0% other ethnicities. Of the total hospital admissions in the country in 2014, about two-thirds were managed by MOH hospitals (66%) followed by 30% in the private hospitals and lastly 4% managed in the remaining eight Ministry of Defence and university hospitals.[8] On HF hospitalizations specifically, unpublished data from the Health Informatics Centre showed that MOH hospitals covered between 77% to 93% of HF hospitalizations in Malaysia when considering only MOH and private hospital data from 2008 to 2016. Because complete patient-level data was required for the trend analysis, we included only hospitalizations from MOH hospitals.

Study population

Patients aged 20 years and above who had incident hospitalizations for HF between January 2007 and December 2016 were eligible for study inclusion. An incident HF hospitalization was defined as a hospitalization with a primary discharge diagnosis of HF without prior admission for HF within the past two years.[9] We used the unique personal identification number (MyKad), previous national identification or passport number for foreign nationalities in combination with date of birth and sex to determine recurrent hospital admissions by a unique patient. Any duplicated records

and records which contained illogical characters or length in the identifier were excluded.

From 2007 to 2016, 157 493 hospitalizations had a primary diagnosis of HF (Supplementary Figure 1). Of these, 1713 hospitalizations had either no unique identifier, incorrect format for the identifier or were duplicate entries. To isolate only incident HF hospitalizations, 50 381 repeat admissions were excluded, leaving 105 399 cases for inclusion in the analysis.

Definitions

HF hospitalization was defined based on a discharge diagnosis of ICD-10 codes of HF which is I50.[10–12] The classification of ethnicity was defined based on the Public Sector Data Dictionary (PSDD) for the Health Informatics Standards (Second edition, Dec 2007) in Malaysia.[13] Ethnicity was recorded as stated by patients or their caregivers based on the categories in the PSDD.[13] They were then categorised into four groups as follows: (i) Malay, (ii) Chinese, (iii) Indian and (iv) other ethnicities which included Peninsular Malaysia, Sabah or Sarawak indigenous groups, Bajau, Kadazan, Murut, Melanau, Kedayan, Iban, Bidayuh, *Bumiputera* Sabah or Sarawak, other ethnic groups and foreign nationalities.

Ethical considerations

Ethics approval was granted by the Medical Research and Ethics Committee, MOH Malaysia (NMRR-19-1108-47994) with permission to use unique identifiers to perform data linkages. Waiver of patient consent was approved because this study was conducted using observational data collected from routine clinical care and all data linkages were performed within the data environment of the Health Informatics Centre. Only aggregated data without identifying information were exported for analysis.

Statistical Analysis

Descriptive statistics on patient demographic characteristics were presented. As missing rates for the unique personal identification number were about 1%, we excluded those observations with missing identification number. For descriptive analysis, continuous data were reported as means with standard deviation (SD) or

median with interquartile range (IQR) while categorical data were reported as frequencies and proportions.

Crude incidence rates by age group, sex and calendar year were calculated by dividing the number of hospitalizations in each category against the respective base population numbers. National population counts by age and sex were extracted from vital statistics data provided by the Department of Statistics Malaysia. To evaluate trends, overall age- and sex-standardised incidence for each calendar year were standardised to the 2016 Malaysian population using direct standardisation. In direct standardisation, the expected incident HF hospitalizations were calculated by multiplying each age-sex specific incidence rate with the proportion of that said age-sex group in the standard population. The standardised incidence rate was then obtained by summing the total expected cases across age categories and dividing by the total in the standard population.[14] An overall age- and sex-standardised incidence rates for each year was also calculated using WHO standard population with direct standardisation.

Finally, to determine the strength and statistical significance of these trends, we used quasi-Poisson models, which accounts for overdispersion of the count data[15]. The population size for each age, sex and ethnicity-specific group were used as the offset variable in the regression. A sensitivity analysis was done to examine the impact of adding ICD-10 codes I11 (hypertensive heart disease with or without HF) and I13 (Hypertensive heart and renal disease with or without HF) when selecting for eligible cases of HF hospitalization. A separate sensitivity analysis was conducted to study the effect of data loss in 2012 and 2013 on the time trends, by excluding these two years from the quasi-Poisson model. All statistical analyses were performed using R statistical software version 3.6.1.[16]

RESULTS

Incidence of HF hospitalization

A total of 105 399 hospital admissions for HF were included from 2007 to 2016. The absolute number of index hospitalizations has increased by 52.3% from 8191 to 12 472 cases annually in this ten-year period. The demographic characteristics of the HF admissions were reported in Table 1. The median age of patients remained stable, from 65.8 (IQR 56.2-74.0) in 2007 to 64.3 (IQR 55.5-73.1) years in 2016. Overall, 55.9%

of the patients were men and they were predominantly Malay (60.9%). Patients of Chinese ethnicity had markedly older age of onset for first HF hospitalizations than all the other ethnic groups.

Crude incidence rates were reported in Table 2. The annual crude incidence rate for HF hospitalization in women was lower than in men (52.8 per 100 000 vs 65.5 per 100 000 population in 2016). This translates into a 23% lower incidence rate in women compared to men, after adjusting for age and calendar year (incidence rate ratio (IRR) 0.77; 95%CI (confidence interval), 0.74-0.80) (Supplementary table 1). Incidence of HF hospitalizations varied widely between ethnicities, where it was highest in Indians, followed by Malays, the other ethnicities group and Chinese (standardised incidence rates were 86.7, 78.9, 60.9 and 32.3 per 100 000 in 2016) (Supplementary table 2). After adjusting for age, sex and calendar year, persons of Indian ethnicity had 20% higher incidence compared to Malays, the largest ethnic group in Malaysia (IRR 1.20, 95% CI 1.14 – 1.26, p-value<0.001) (Supplementary table 3) By age, incidence rate peaked at the 80 to <85 years category while the lowest incidence rate was in the youngest age category (20 to <25 years).

Trends on incident HF hospitalization

The overall rate of incident HF hospitalization declined by 1% annually after accounting for age and sex (IRR per calendar year 0.99 (95% CI, 0.982-0.996), p-value = 0.003). The rate of decline in incidence rates were proportional for men and women (Figure1) and the corresponding age-adjusted interaction term between calendar year and sex also showed no difference (p-value= 0.347). Upon stratification by age, the trend lines for incidence in men and women overlapped at the youngest ages but began to separate from the 40 to <45 years category, where men showed a slightly quicker rise in incidence (Figure 2). Then, the incidence rates stabilised for ages 50 to <60 for both sex groups followed by declines from age 60 years onwards. This reduction in women appeared to level off from the age category of 75 to <80 onwards whilst incidence rates for men continued to decline.

Next, Figure 3 contrasted the ten-year difference in incidence by age group and sex. In men, a slight increase in incidence was seen between age 30 to 65 years. This was in contrast to the drop observed from age 65 years onwards, with the most apparent lowering of incidence in the peak ages, i.e., the 80 to <85-year age group (a difference in incidence = 467.2- 553.6= -86.4 per 100 000). Although a similar

decline amongst women was noticeable in those aged above 65 years, the incidence for those in the 80 - <85 age group has, in contrast to men, grown higher in 2016 compared to 2007 (difference in incidence = 532.5 – 445.3 = +87.2 cases per 100 000). A separate figure contrasting this difference in different ethnic groups was also included in the supplementary material (Supplementary figure 2)

We found that decreases in age-standardised incidence of HF hospitalization with calendar year differed by ethnicity (Fig 4). Only the Indians exhibited a significant annual decrease of 3% (p-value = 0.049) in HF hospitalization compared to the other ethnicities. Within each ethnic subgroup, men had distinctly higher incidence than women. The exception was for Indians, where the women had similar crude incidence and trends as their male counterparts (Supplementary figure 3).

Table 1. Demographic characteristics of patients with incident heart failure hospitalizations

Year	2007 (N = 8191)		2008 (N = 10741)		2009 (N = 10513)		2010 (N = 10551)		2011 (N = 11426)	
	n	%	n	%	n	%	n	%	n	%
Age group (years)										
20-<25	45	0.5	54	0.5	50	0.5	63	0.6	55	0.5
25-<30	60	0.7	87	0.8	83	0.8	88	0.8	104	0.9
30-<35	95	1.2	124	1.2	125	1.2	141	1.3	139	1.2
35-<40	148	1.8	180	1.7	162	1.5	196	1.9	223	2.0
40-<45	238	2.9	337	3.1	345	3.3	362	3.4	374	3.3
45-<50	463	5.7	660	6.1	635	6.0	617	5.8	717	6.3
50-<55	774	9.4	1041	9.7	987	9.4	961	9.1	1135	9.9
55-<60	916	11.2	1312	12.2	1310	12.5	1289	12.2	1457	12.8
60-<65	1134	13.8	1469	13.7	1448	13.8	1588	15.1	1631	14.3
65-<70	1235	15.1	1498	13.9	1474	14.0	1457	13.8	1515	13.3
70-<75	1234	15.1	1635	15.2	1630	15.5	1554	14.7	1621	14.2
75-<80	918	11.2	1188	11.1	1086	10.3	1125	10.7	1236	10.8
80-<85	582	7.1	702	6.5	713	6.8	707	6.7	746	6.5
85+	349	4.3	454	4.2	465	4.4	403	3.8	473	4.1
Sex										
Men	4556	55.6	5903	55.0	5838	55.5	5905	56.0	6302	55.2

Table 1 (continued). Demographic characteristics of patients with incident heart failure hospitalizations

Year	2007 (N = 8191)		2008 (N = 10741)		2009 (N = 10513)		2010 (N = 10551)		2011 (N = 11426)	
	n	%	n	%	n	%	n	%	n	%
Ethnicity										
Malay	4837	59.1	6396	59.5	6456	61.4	6276	59.5	6964	60.9
Chinese	1593	19.4	1929	18.0	1950	18.5	2018	19.1	2090	18.3
Indian	801	9.8	1381	12.9	1201	11.4	1154	10.9	1337	11.7
Others	887	10.8	1035	9.6	901	8.6	892	8.5	1026	9.0
Missing	73	0.9			5	0.0	211	2.0	9	0.1
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (years)	65.8	56.2-	65.4	55.9-	65.3	56.1-	64.9	55.9-	64.6	55.4-
By ethnicity										
Malay	65.1	56.0-	64.5	55.6-	64.7	55.9-	64.2	55.7-	64.1	55.2-
Chinese	69.7	60.7-	69.9	60.6-	69.9	60.3-	69.9	60.5-	69.9	60.6-
Indian	61.8	53.1-	61.3	52.6-	61.8	53.6-	61.7	53.8-	61.9	54.1-
Others	65.8	56.1-	66.5	54.0-	65.0	53.2-	65.1	55.3-	63.0	51.6-

Table 1 (continued, 2012-2016). Demographics characteristics of patients with incident heart failure hospitalizations

Year	2012 (N = 8077)		2013 (N = 9727)		2014 (N = 11328)		2015 (N = 12373)		2016 (N = 12472)	
	n	%	n	%	n	%	n	%	n	%
Age group (years)										
20-<25	37	0.5	42	0.4	66	0.6	59	0.5	59	0.5
25-<30	80	1.0	82	0.8	104	0.9	117	0.9	97	0.8
30-<35	96	1.2	136	1.4	163	1.4	176	1.4	191	1.5
35-<40	161	2.0	189	1.9	239	2.1	285	2.3	318	2.5
40-<45	267	3.3	329	3.4	411	3.6	459	3.7	461	3.7
45-<50	494	6.1	553	5.7	691	6.1	776	6.3	754	6.0
50-<55	763	9.4	910	9.4	1046	9.2	1139	9.2	1125	9.0
55-<60	1059	13.1	1241	12.8	1521	13.4	1592	12.9	1585	12.7
60-<65	1172	14.5	1481	15.2	1709	15.1	1831	14.8	1913	15.3
65-<70	1151	14.3	1332	13.7	1593	14.1	1817	14.7	1840	14.8
70-<75	1033	12.8	1287	13.2	1328	11.7	1497	12.1	1549	12.4
75-<80	908	11.2	1097	11.3	1294	11.4	1345	10.9	1267	10.2
80-<85	530	6.6	630	6.5	702	6.2	790	6.4	838	6.7
85+	326	4.0	418	4.3	461	4.1	490	4.0	475	3.8
Sex										
Men	4506	55.8	5406	55.6	6368	56.2	6965	56.3	7117	57.1

Table 1 (continued, 2012-2016). Demographics characteristics of patients with incident heart failure hospitalizations

Year	2012 (N = 8077)		2013 (N = 9727)		2014 (N = 11328)		2015 (N = 12373)		2016 (N = 12472)	
	n	%	n	%	n	%	n	%	n	%
Ethnicity										
Malay	5138	63.6	5922	60.9	6915	61.0	7605	61.5	7637	61.2
Chinese	1381	17.1	1778	18.3	1986	17.5	2232	18.0	2201	17.6
Indian	786	9.7	1018	10.5	1266	11.2	1280	10.3	1305	10.5
Others	772	9.6	1009	10.4	1147	10.1	1256	10.2	1329	10.7
Missing					14	0.1				
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (years)	64.5	55.6-73.9	64.7	55.8-74.0	64.2	55.4-73.5	64.3	55.3-	64.3	55.5-73.1
By ethnicity										
Malay	64.2	55.7-72.9	63.8	55.5-72.7	63.5	55.2-72.0	63.5	55.0-	63.6	55.0-71.5
Chinese	69.6	59.8-77.7	70.8	61.4-78.6	69.9	60.1-78.0	70.1	60.6-	70.0	61.2-78.4
Indian	61.3	54.3-71.3	61.9	54.0-70.8	61.9	54.6-71.2	61.9	52.6-	61.5	54.1-70.2
Others	62.5	50.6-73.5	63.9	51.9-74.1	62.0	50.5-72.8	63.0	52.0-	62.4	52.0-73.4

Table 2. Incidence of heart failure hospitalizations by age and sex

		2007		2008		2009		2010		2011	
Sex	**Age (years)**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**
Male	20-<25	24	1.7	30	2.0	25	1.7	33	2.2	29	1.9
	25-<30	38	3.1	52	3.9	47	3.3	51	3.4	54	3.6
	30-<35	57	5.5	74	6.9	75	6.8	80	6.9	92	7.6
	35-<40	88	9.3	98	10.2	96	9.7	113	11.1	144	13.9
	40-<45	152	17.3	216	24.3	210	23.4	240	26.4	251	27.2
	45-<50	280	36.1	388	48.5	376	45.8	396	47.1	451	52.8
	50-<55	491	77.5	623	94.8	641	94.1	595	84.2	714	97.5
	55-<60	561	114.6	821	161.0	831	157.3	800	146.3	878	153.8
	60-<65	685	198.4	849	230.3	873	221.9	936	224.6	951	218.0
	65-<70	699	279.6	847	332.5	825	316.9	803	297.0	851	299.6
	70-<75	619	370.7	818	454.4	819	426.6	831	414.1	828	402.3
	75-<80	426	429.4	537	534.9	488	472.0	516	469.1	555	484.3
	80-<85	289	553.6	334	586.0	322	529.6	331	520.4	329	519.7
	85+	147	399.5	216	577.5	210	542.6	180	416.7	175	412.7
	All ages	4556	54.4	5903	68.1	5838	65.1	5905	63.7	6302	66.5
	WHO standardized	-	79.6	-	98.2	-	92.6	-	89.1	-	91.4
Female	20-<25	21	1.6	24	1.8	25	1.8	30	2.1	26	1.8
	25-<30	22	2.0	35	3.0	36	2.9	37	2.8	50	3.7
	30-<35	38	3.9	50	5.1	50	5.1	61	6.0	47	4.4
	35-<40	60	6.6	82	8.9	66	7.1	83	8.8	79	8.3
	40-<45	86	10.3	121	14.2	135	15.5	122	13.8	123	13.7

Table 2 (continued). Incidence of heart failure hospitalizations by age and sex

		2007		2008		2009		2010		2011	
Sex	**Age (years)**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**
	45-<50	183	25.2	272	36.7	259	34.2	221	28.5	266	33.5
	50-<55	283	47.5	418	67.5	346	53.9	366	55.1	421	61.3
	55-<60	355	76.5	491	101.5	479	95.6	489	94.2	579	106.6
	60-<65	449	136.1	620	174.6	575	150.6	652	160.3	680	159.3
	65-<70	536	214.8	651	258.2	649	252.6	654	244.4	664	234.5
	70-<75	615	342.0	817	426.9	811	402.5	723	346.6	793	370.0
	75-<80	492	419.1	651	553.6	598	502.9	609	493.5	681	527.9
	80-<85	293	445.3	368	508.3	391	504.5	376	465.9	417	513.5
	85+	202	402.4	238	471.3	255	500.0	223	391.9	298	517.4
	All ages	3635	45.9	4838	59.3	4675	55.6	4646	53.6	5124	57.6
	WHO standardized	-	63.0	-	80.0	-	74.8	-	70.9	-	75.5

Incidences are per 100 000 population.

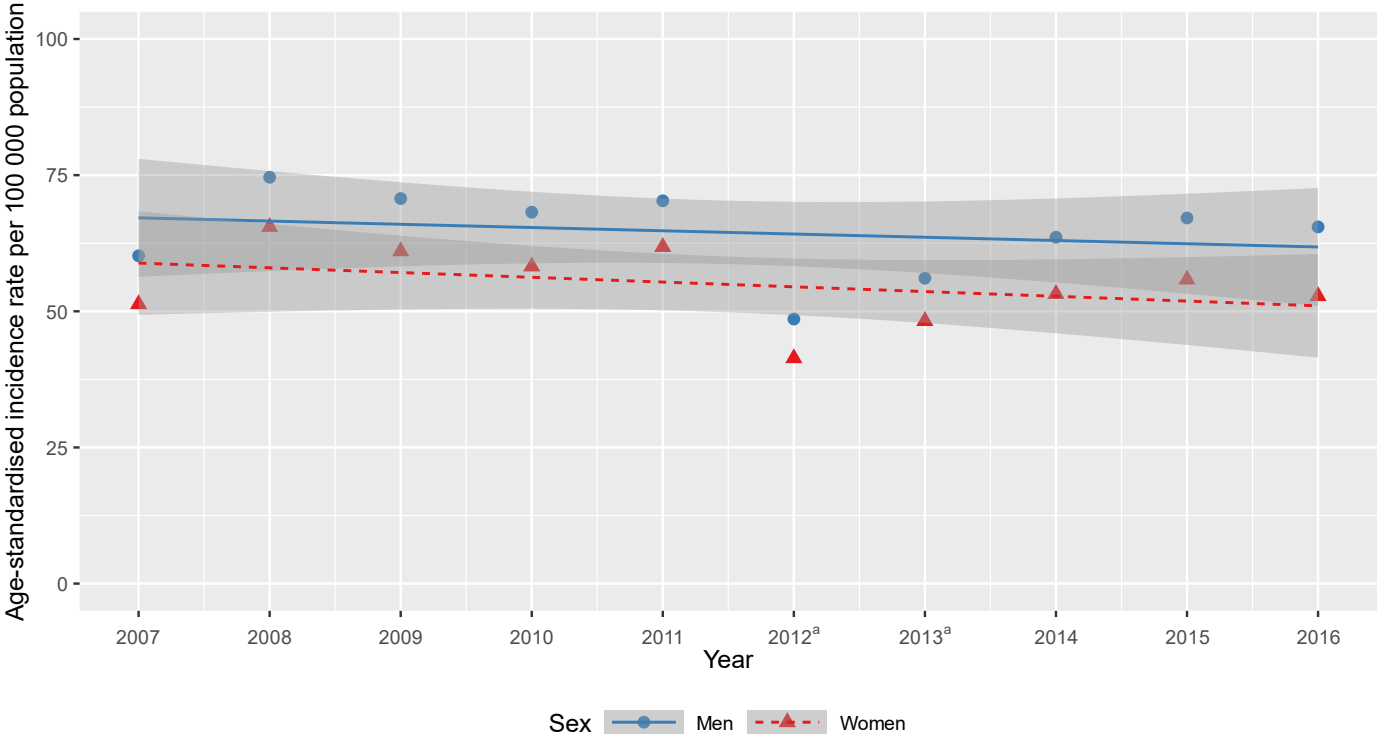
Table 2 (continued, 2012-2016). Incidence of heart failure hospitalizations by age and sex

		2012		2013		2014		2015		2016	
Sex	**Age (years)**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**
Male	20-<25	18	1.2	28	1.9	36	2.4	38	2.5	40	2.3
	25-<30	44	2.9	51	3.4	60	4.0	74	5.0	63	3.7
	30-<35	66	5.2	78	5.8	113	8.0	108	7.5	126	8.6
	35-<40	105	10.0	121	11.3	159	14.5	199	17.6	219	18.6
	40-<45	163	17.4	209	21.9	264	27.2	306	31.0	314	31.8
	45-<50	304	35.3	357	41.1	441	50.4	500	56.6	495	56.7
	50-<55	474	62.7	574	73.8	678	85.2	755	93.1	755	93.0
	55-<60	662	111.3	769	124.0	941	145.9	961	143.7	1012	147.7
	60-<65	665	147.3	886	190.1	1000	207.6	1069	213.7	1094	209.1
	65-<70	657	217.2	740	228.7	887	258.0	1031	285.7	1009	260.1
	70-<75	544	263.4	648	314.7	689	330.6	739	341.5	800	335.7
	75-<80	436	347.1	499	363.7	607	416.3	637	425.2	636	406.9
	80-<85	232	363.6	283	440.1	302	450.7	344	473.2	363	467.2
	85+	136	300.2	163	333.3	191	362.4	204	363.6	191	292.5
	All ages	4506	46.5	5406	54.7	6368	63.1	6965	67.7	7117	65.5
WHO standardised		-	63.2	-	72.8	-	81.9	-	86.2	-	83.8
Female	20-<25	19	1.3	14	1.0	30	2.1	21	1.5	19	1.2
	25-<30	36	2.6	31	2.2	44	3.2	43	3.1	34	2.3
	30-<35	30	2.7	58	4.9	50	4.0	68	5.3	65	4.9
	35-<40	56	5.9	68	7.1	80	8.2	86	8.5	99	9.4
	40-<45	104	11.5	120	13.1	147	15.9	153	16.5	147	15.8

Table 2 (continued, 2012-2016). Incidence of heart failure hospitalizations by age and sex

		2012		2013		2014		2015		2016	
Sex	**Age (years)**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**	**n**	**Incidence**
	45-<50	190	23.3	196	23.4	250	29.2	276	31.7	259	29.8
	50-<55	289	41.0	336	46.5	368	49.7	384	50.6	370	47.9
	55-<60	397	69.9	472	79.4	580	93.5	631	98.0	573	86.8
	60-<65	507	114.7	595	130.5	709	150.3	762	155.3	819	158.2
	65-<70	494	162.8	592	181.2	706	202.2	786	213.5	831	209.3
	70-<75	489	227.7	639	298.3	639	294.5	758	335.8	749	297.6
	75-<80	472	337.6	598	394.2	687	427.0	708	427.8	631	361.8
	80-<85	298	368.4	347	432.1	400	487.2	446	510.3	475	532.5
	85+	190	305.5	255	377.2	270	370.9	286	369.5	284	386.9
	All ages	3571	39.2	4321	46.3	4960	52.0	5408	55.5	5355	52.8
	WHO standardised	-	50.4	-	59.0	-	64.8	-	68.1	-	64.4

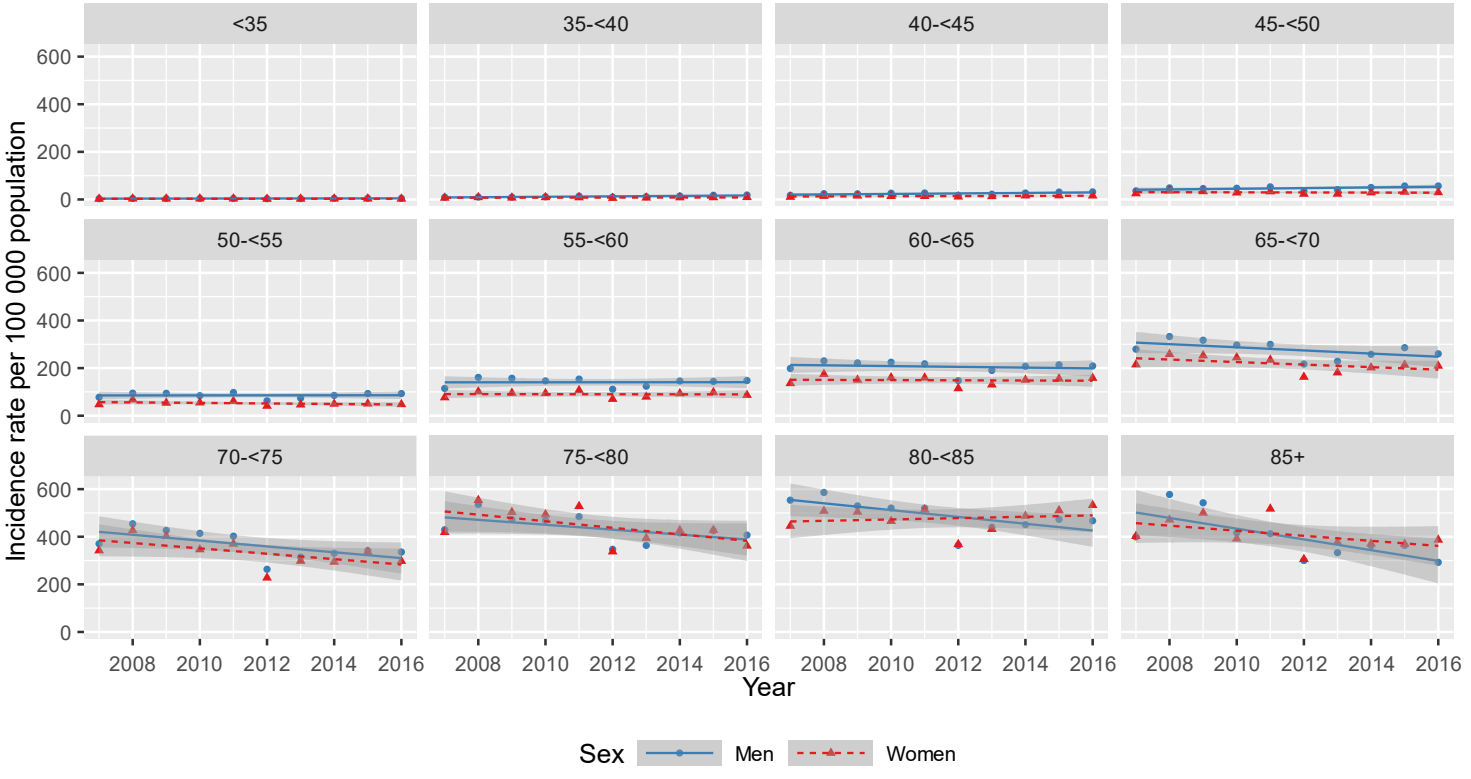
Incidences are per 100 000 population.



a. Some data loss occured in 2012 & 2013 during a data migration process

Sex	2007	2008	2009	2010	2011	2012[a]	2013[a]	2014	2015	2016
Male	60.2	74.6	70.7	68.2	70.3	48.6	56.1	63.6	67.1	65.5
Female	51.3	65.5	61.0	58.2	61.8	41.4	48.2	53.2	55.8	52.8

Figure 1. Trends in incidence for heart failure hospitalizations, standardised against the 2016 Malaysian population



[a.] Some data loss occured in 2012 & 2013 during a data migration process

Figure 2. Trends of incidence for heart failure hospitalizations for men and women by age categories

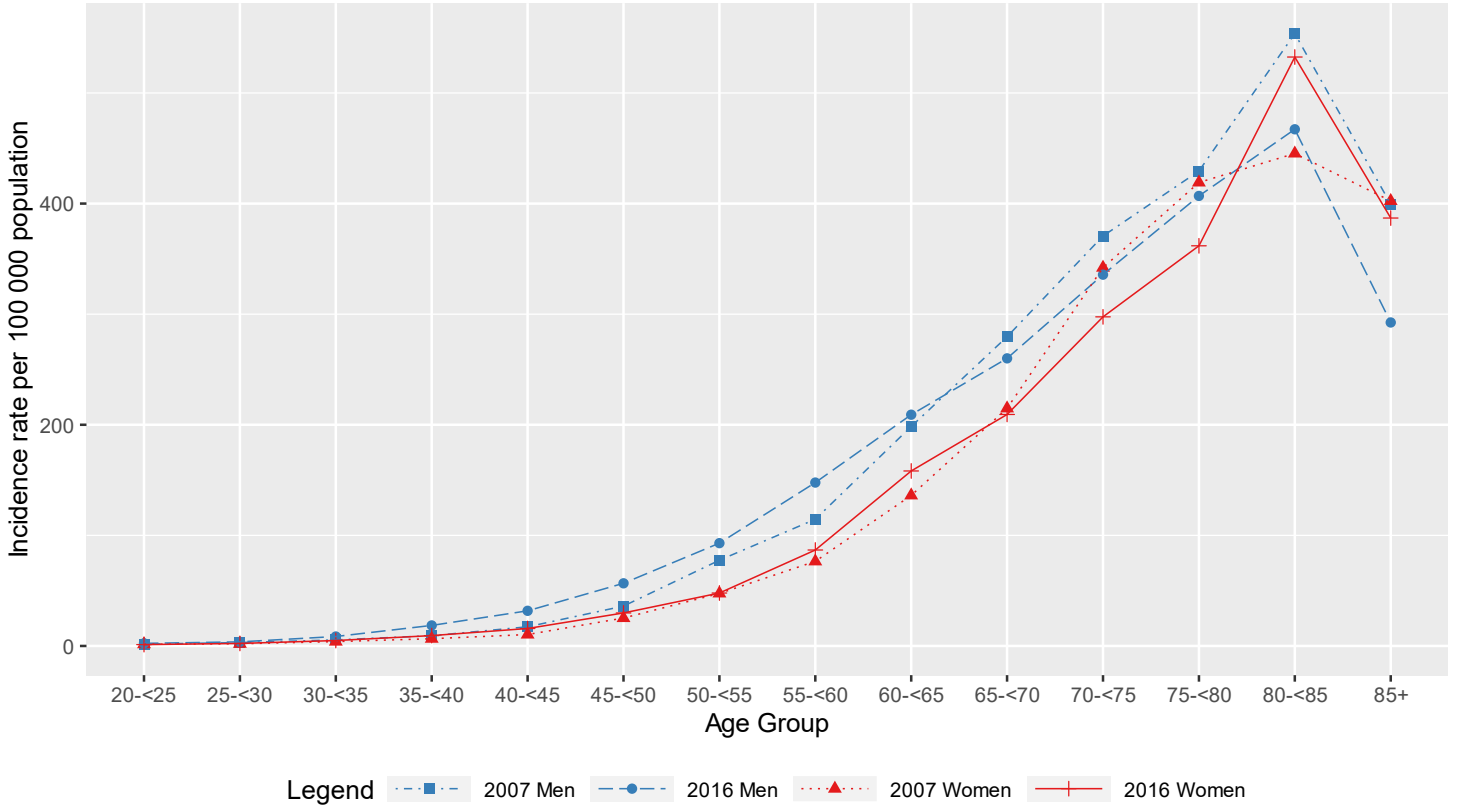
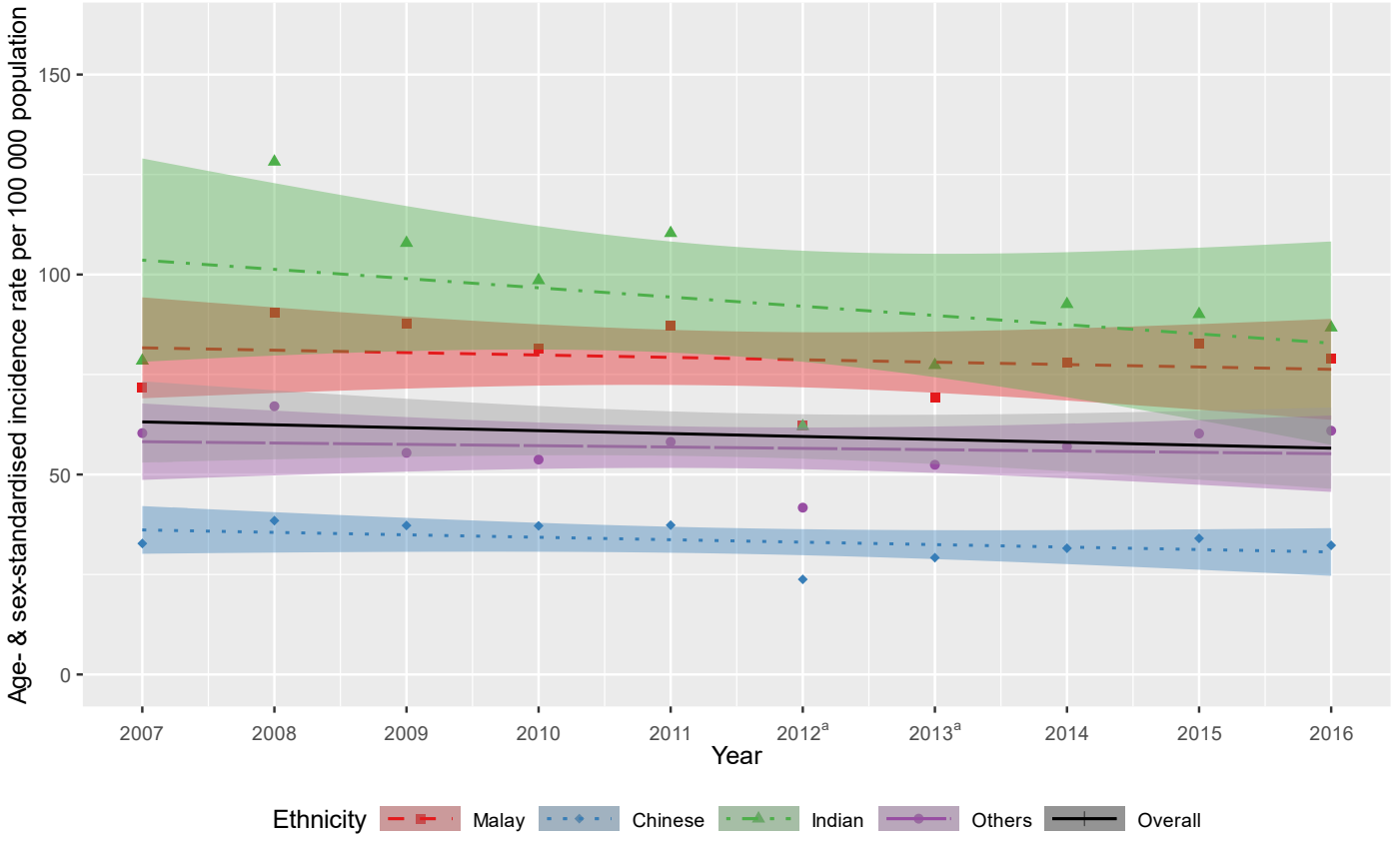


Figure 3. Trends of incidence rate by age and sex, comparing 2007 and 2016



a. Some data loss occured in 2012 & 2013 during a data migration process

Figure 4. Trends for heart failure incidence by ethnicity

DISCUSSION

We presented several findings here using data from a national hospital discharge database in Malaysia. First, comparisons by sex have revealed that women had persistently lower incidence rates of HF hospitalization compared to men but both experienced similar reductions across time. Second, we found that the age-standardised incidence rates for HF hospitalizations have been declining at an annual rate of 1%. This decline was driven by patient older than 65 years. However, the absolute burden has increased by a-third in ten years. Third, we found that Malaysian patients of Indian ethnicity had distinctly higher incidence rates and younger age of onset than other ethnic groups but also exhibited greater decline in incidence compared to other ethnicities. Another noteworthy finding was that lower incidence rates in women was not observed in this ethnic subgroup.

This study is among the first to report on the time trends of incident HF hospitalizations in Asia. The closest data available for comparison was the total HF hospitalizations (i.e. not restricted to incident cases) for Singapore, a neighbouring country with an ethnic diversity and health system comparable to Malaysia.[17,18] The authors found that the burden of HF hospitalizations was increasing by 38% from 1991 to 1998.[17,18] A decade later, we have found that the incidence of HF hospitalizations has been steadily decreasing irrespective of sex. This gradual decline is consistent to those reported in industrialized countries including Australia, the Netherlands and Scotland which saw HF hospitalizations peak and declining since the early 1990s.[19–21] These findings potentially reflect the doubling of percutaneous coronary intervention rates and increase in use of secondary preventive medications after myocardial infarction, thus contributing to an overall reduction in risk of HF hospitalization. [22,23] Further, a smaller extent of this decrease in incidence can be explained by improvements in the awareness, treatment and control of classical risk factors such as that seen in hypertension.[24]

Men had consistently higher incidence of HF hospitalization compared to women. In relation to risk factors, tobacco smoking appears to explain a large extent of higher risks of HF hospitalization in men with a 30-fold higher current smoking prevalence than women (43.0% versus 1.4% among persons >18 years in 2015) whereas risk factors such as diabetes and hypertension were largely comparable between men and women.[25,26] For other metabolic risk factors however, women

present with higher prevalence of hypercholesterolaemia and obesity (50.7% vs 43.5% and 33.6% vs 27.8% for hypercholesterolaemia and obesity compared to men). Similar elevated rates of HF hospitalization in men compared to women were observed in other countries.[20,27] Thus, public health strategies aimed to mitigate tobacco exposure in men could provide effective means to reduce CVD burden, including HF hospitalization.

Compared to industrialised countries, Malaysian HF patients experience earlier onset of new HF hospitalizations compared to patients in Australia and the United States (mean age range 63.6 – 64.8 years vs 73.3- 74.2 years). [19,28] Next, our study confirms and extends the findings from other studies that the incidence of HF hospitalization increases with each age strata up to the 80 to <85 age group.[19] A sharp drop in incidence of HF hospitalization among the eldest group might be due to their often complex comorbidities and presentation with gradual onset of symptoms or lack of typical ones such as shortness of breath. [29] Concomitant conditions such as mobility issues further complicates diagnosis, resulting in HF being diagnosed as secondary diagnoses instead of primary diagnosis. [29,30] This ten-year study period has seen changes in the HF hospitalization incidence that differed by age. Firstly, steady declines were seen in both men and women above the age of 65 years and this can be attributed to more active screening and treatment of cardiovascular risk factors in older persons and improved quality of care after acute coronary syndrome. It is also possible that middle-aged and older patients are increasingly being hospitalized for other primary diagnoses such as pneumonia and influenza, with HF being the secondary diagnosis.[31] Secondly, in contrast to the decrease in incidence among older persons, we observed a slight increase in incidence among men in the younger ages of 30 to 65 years. This suggests a shift to earlier onset of atherosclerotic disease in the population, which is likely given the high underlying prevalence of atherogenic risk factors.[25] What is more worrying is the large proportion of these patients who were not diagnosed and treated. In 2011, the National Health and Morbidity survey found that about half of the patients with diabetes and 75% of those with hypercholesterolaemia were undiagnosed.[32] Another noteworthy point is the slowing decrease in incidence among women older than 80 years compared to the men. Possible explanations include greater longevity in women and increase in readiness to diagnose HF with preserved ejection fraction, which is more prevalent in older women.[33]

We found distinct ethnic differences in incidences for HF hospitalization, where Malaysians of Indian ethnicity present with the highest incidence and with earlier onset. This result coincides with a recent published review that shown people of South Asian origins were at higher risk of developing HF and at a younger age, compared to the other ethnic groups.[34] Elevated risks of ischaemic heart disease amongst both South Asians and people of South Asian descent have been described and characterised by high rates of glucose intolerance, hyperinsulinaemia, central obesity and raised fasting lipids.[35,36] Indeed, higher prevalence of diabetes and abdominal obesity in this subpopulation is known in Malaysia (prevalence of 34.9% and 63.5% in Indians vs 15.2% and 45.4% in the overall population).[32] Another notable finding from this study is the diminished protective effect of being female for the Indian subgroup; i.e. the women have the same risks for first HF hospitalization as Indian men. Given that being overweight or obese and low levels of physical activity were more prevalent amongst women in this ethnic subgroup[37,38], it appears that this cardiometabolic feature plays a substantial role to overall risk of developing downstream HF. Nonetheless, we have shown that incidence in this group is declining more rapidly than the others, indicating that these background risks were amenable to treatment and lifestyle modifications. Lastly, part of the observed ethnic differences in HF hospitalization rates may be partly explained by socioeconomic differences, where the Chinese, who had the lowest incidence were more socioeconomically advantaged compared to other ethnic groups which in turn impacts living conditions, lifestyle and dietary choices.[22,39]

Implications for practice and policy

Malaysia is among several high-performing Southeast Asian countries which set out to reform their health care systems.[18] Hospitalization for HF poses substantial economic burden to its healthcare expenditure.[40] We have shown that the incidence of HF hospitalization was decreasing in parallel with an increase in absolute counts of new cases. From the clinical practice viewpoint, this reduction in incidence is likely a reflection of increase in guideline-adherent management after myocardial infarction together with a smaller extent in improvements in control of cardiovascular risk factors.[24,41] From the policy perspective, clear gaps in the healthcare resources supply-demand chain exists as the HF disease burden escalates; through a combination of increasing new cases and prolonged survival of existing patients. This

is expected to place additional strain on the limited capacity of cardiology services in Malaysia, which for instance, has eight cardiologists per million population in 2013 as opposed to forty per million population in Singapore.[42,43]

While epidemiological transitions were well-documented in western countries, it is likely that challenges are heightened in Asia due the dual infectious and non-communicable disease burden, shift to sedentary occupations and dietary changes.[44] Dietary habits in Malaysia have evolved as a direct consequence of urbanisation and higher incomes and can be characterised by rising trends of daily caloric intake, increase in the consumption of fats, oil, sugar and processed food.[45] Surveillance on traditional risk factors have revealed worrying trends in the community prevalence of diabetes, central obesity, hypercholesterolaemia. From the public health viewpoint, population-wide benefits can be instilled though multi-faceted initiatives including the use of mass and social media to advocate the consumption of healthier food options and increased physical activity, economic subsidies on fresh vegetables and fruits, school- and workplace-based health programmes.[46]

As some subgroups within the population are more susceptible to develop HF, targeted approaches to detecting and treating risk factors may be efficient measures to minimise overall population risks. In men, it appears that smoking is the major modifiable risk factor which drives the risk of cardiovascular events. Locally, a nationwide ban on all forms of smoking in all eateries in Malaysia has been in force since 2019 and it remains to be determined if this policy indeed leads to reductions in the incidence of cardiovascular diseases among men.[47] A 2017 clinical practice guideline for primary prevention of cardiovascular diseases has incorporated a recommendation for lowered age cut-off at 30 years for opportunistic screening for cardiovascular risk.[48] As resources are finite, the more cost-efficient move would be to perform targeted risk stratification, for instance early cardiovascular screening in adolescents and young adults who are at higher risk such as Indian women, than mass screening.[49]

Strengths and limitations

Among the strengths of this study was the use of a large hospitalization dataset and the availability of information over a span of ten years, which allowed us to stratify and examine incidence by demographic categories. There were several limitations in

this study. First, there was the lower data coverage in 2012 and 2013 due to some loss of information from several centres during a data migration process. This data loss did not occur at random hence imputation was not a viable option. To get a complete picture of the prevalence of HF in Malaysia, outpatient visits for HF should ideally be included but data for outpatient and specialist clinics' data was only available in aggregate form by ICD-10 codes which encompassed a broader scope of circulatory disease, not HF specifically. Another limitation was the underestimation of absolute numbers of hospitalizations because only a primary discharge diagnosis of HF was considered for inclusion and cases came from only MOH hospitals. Additionally, the use of overall population as denominator will also underestimate the rate of hospitalization. The primary discharge diagnosis was coded with ICD-10 code, however only the category level of the code was reliable, limiting the possibility of identifying the subtypes and aetiology of HF using the ICD-10 code. In addition, the lack of information on drug therapies meant that we were not able the quantify the effect of newer HF drug therapy on hospitalization during the study period. Nevertheless, this was the best available data that allowed uniform assessment of trend changes and this was not influenced by the selection criteria. Lastly, information on left ventricular function, comorbid conditions and other relevant risk factors were also not available for differentiating between aetiologies and subtypes of HF.

CONCLUSION

This population-based analysis has shown a steady decrease in incidence of HF hospitalizations over a period of ten years. Incidence was lower in women than men and persons of Indian ethnicity compared to other ethnic groups. These findings highlight disparities in occurrence of HF between sex and ethnic groups in the population that were attributable to underlying population risks and offers opportunities for targeted interventions in reducing the risk of de novo HF hospitalization.

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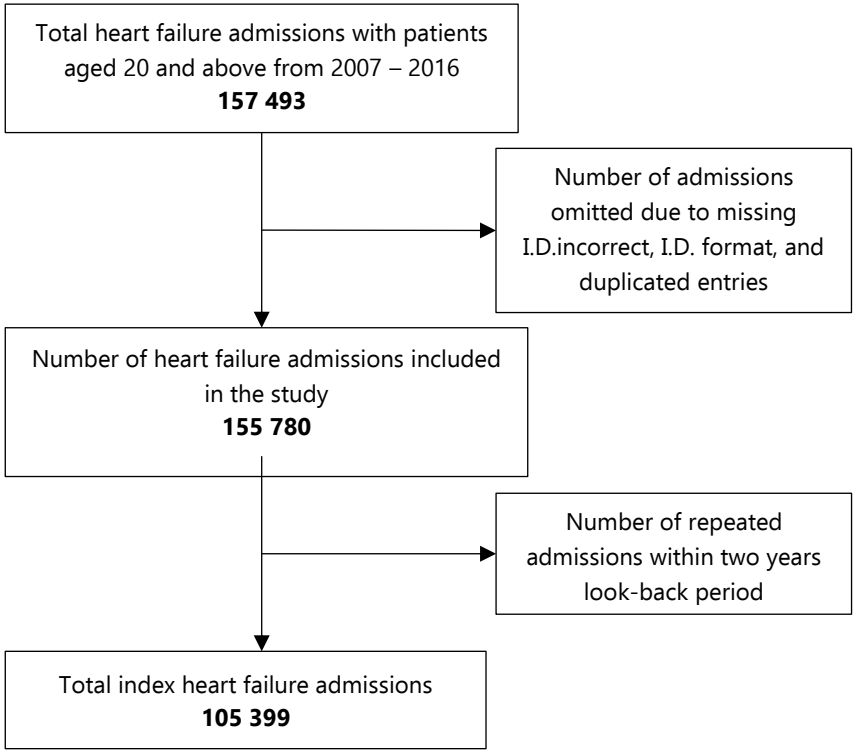
SUPPLEMENTARY MATERIAL



Supplementary figure 1. Identification and inclusion of HF hospitalizations

Supplementary table 1. Quasi-Poisson regression analysis with (i) only time, (ii) time, sex and age and (iii) age and an interaction term between time and sex

	Unadjusted model			**Model with time, sex and age**			**Model with age and interaction term between sex and time**		
Predictors	Incidence Rate Ratios	CI	p	Incidence Rate Ratios	CI	p	Incidence Rate Ratios	CI	p
Intercept	0.56	0.35 – 0.88	**0.016**	0.02	0.02 – 0.03	**<0.001**	0.02	0.02 – 0.03	**<0.001**
Time	1.00	0.93 – 1.08	0.968	0.99	0.982-0.996	**0.003**	0.99	0.98 – 1.00	0.102
Time: Women							0.99	0.98 – 1.01	0.347
Women				0.77	0.74 – 0.80	**<0.001**	0.80	0.73 – 0.88	**<0.001**
Age, in years (ref =20-<25)									
25-<30				1.79	1.26 – 2.57	**0.002**	1.79	1.26 – 2.57	**0.002**
30-<35				3.22	2.33 – 4.54	**<0.001**	3.22	2.33 – 4.53	**<0.001**
35-<40				5.77	4.25 – 8.01	**<0.001**	5.77	4.25 – 8.00	**<0.001**
40-<45				10.85	8.10 – 14.87	**<0.001**	10.85	8.10 – 14.86	**<0.001**

Supplementary table 1 (continued). Quasi-Poisson regression analysis with (i) only time, (ii) time, sex and age and (iii) age and an interaction term between time and sex

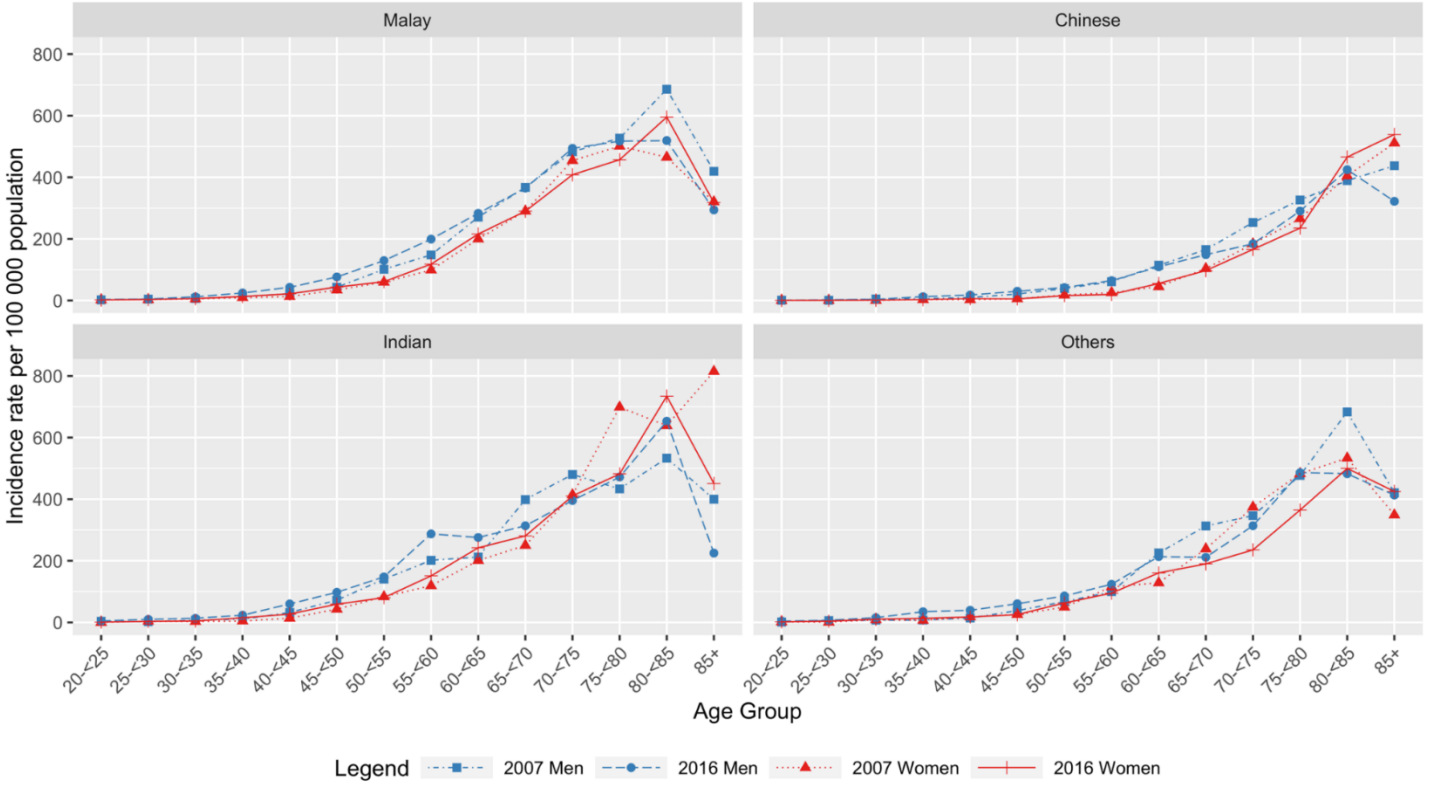
	Unadjusted model			**Model with time, sex and age**			**Model with age and interaction term between sex and time**		
Predictors	Incidence Rate Ratios	CI	p	Incidence Rate Ratios	CI	p	Incidence Rate Ratios	CI	p
45-<50				21.32	16.08 – 28.99	**<0.001**	21.33	16.08 – 28.98	**<0.001**
50-<55				38.30	29.00 – 51.87	**<0.001**	38.29	29.01 – 51.84	**<0.001**
55-<60				64.26	48.76 – 86.89	**<0.001**	64.26	48.78 – 86.85	**<0.001**
60-<65				98.59	74.87 – 133.21	**<0.001**	98.59	74.90 – 133.15	**<0.001**
65-<70				136.30	103.49 – 184.20	**<0.001**	136.31	103.53 – 184.12	**<0.001**
70-<75				193.36	146.79 – 261.34	**<0.001**	193.35	146.83 – 261.21	**<0.001**
75-<80				243.49	184.58 – 329.49	**<0.001**	243.47	184.63 – 329.31	**<0.001**
80-<85				271.50	204.87 – 368.76	**<0.001**	271.45	204.91 – 368.53	**<0.001**
85+				225.18	168.75 – 307.59	**<0.001**	225.16	168.80 – 307.43	**<0.001**
Observations	280			280			280		
Deviance	216444.951			2916.594			2906.844		

Supplementary table 2. Standardised incidence of heart failure hospitalizations per 100 000 population by sex and ethnicity.

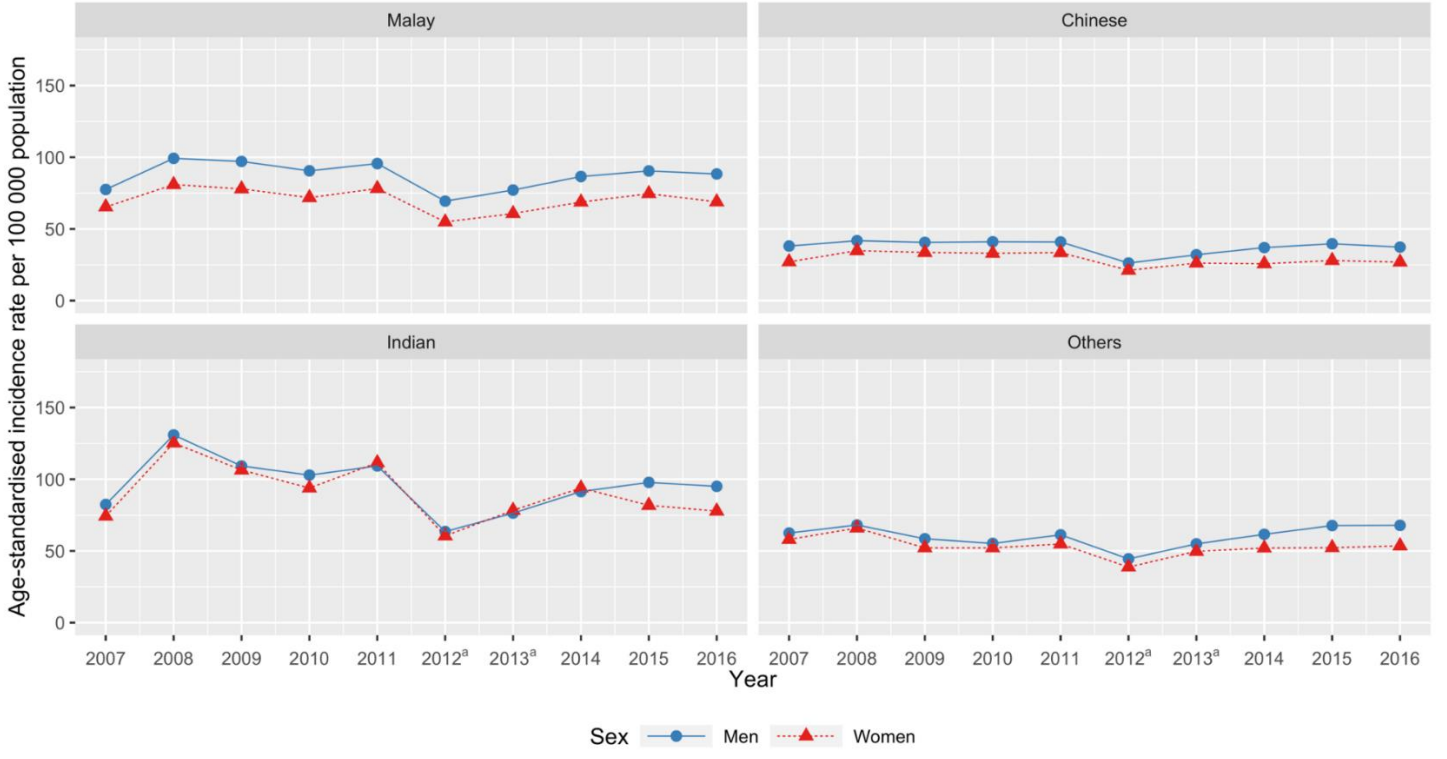
Sex	Ethnicity	Standard population	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Both	All	Malaysia	55.9	70.2	66.0	63.4	66.2	45.1	52.3	58.6	61.7	59.4
		WHO	71.3	89.1	83.7	80.0	83.5	56.8	65.9	73.3	77.1	74.1
	Malay	Malaysia	71.6	90.4	87.8	81.5	87.2	62.4	69.2	78.0	82.8	78.9
		WHO	90.7	114.0	110.7	102.3	109.2	78.2	86.4	96.9	102.5	97.8
	Chinese	Malaysia	32.8	38.5	37.3	37.2	37.3	23.8	29.2	31.6	34.0	32.3
		WHO	43.2	50.5	48.7	48.6	48.9	31.0	38.5	41.1	44.4	42.1
	Indian	Malaysia	78.4	128.2	107.9	98.5	110.3	62.0	77.3	92.6	90.1	86.7
		WHO	98.6	159.6	134.7	122.4	137.6	77.0	95.5	115.1	111.5	106.2
	Others	Malaysia	60.3	67.1	55.4	53.7	58.2	41.7	52.4	57.0	60.2	60.9
		WHO	77.1	85.6	70.0	67.4	72.5	51.8	65.9	70.3	75.1	75.4
Male	Malay	Malaysia	77.5	99.2	97.1	90.5	95.6	69.4	77.1	86.6	90.4	88.4
		WHO	102.0	129.8	126.8	118.0	123.6	90.1	99.3	110.8	114.9	112.4
	Chinese	Malaysia	38.1	41.8	40.7	41.1	41.0	26.2	32.0	37.0	39.7	37.3
		WHO	51.6	56.7	54.3	54.9	54.7	34.9	43.0	49.1	52.8	49.6
	Indian	Malaysia	82.4	130.9	109.2	102.9	109.3	63.5	76.4	91.4	97.8	95.0
		WHO	105.8	167.4	140.2	131.5	140.1	80.7	96.5	116.1	124.1	118.5
	Others	Malaysia	62.5	68.1	58.5	55.2	61.2	44.5	54.9	61.6	67.7	67.8
		WHO	83.2	91.0	76.9	71.8	79.1	57.4	72.0	78.0	87.3	86.4

Supplementary table 2 (continued). Standardised incidence of heart failure hospitalizations per 100 000 population by sex and ethnicity.

Sex	Ethnicity	Standard population	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Female	Malay	Malaysia	65.4	80.9	77.9	71.9	78.2	54.9	60.7	68.7	74.6	68.9
		WHO	79.5	98.2	94.7	86.6	94.7	66.4	73.6	83.0	90.1	83.3
	Chinese	Malaysia	27.1	34.9	33.6	33.0	33.5	21.2	26.2	25.7	28.0	26.9
		WHO	34.7	44.3	43.2	42.3	43.0	27.2	34.1	33.0	36.1	34.6
	Indian	Malaysia	74.3	125.3	106.4	93.9	111.5	60.5	78.4	93.9	81.8	77.8
		WHO	91.4	151.8	129.3	113.3	135.0	73.4	94.4	114.1	98.8	94.0
	Others	Malaysia	58.1	66.0	52.1	52.1	54.9	38.8	49.8	52.0	52.3	53.6
		WHO	71.0	80.3	63.1	63.0	66.0	46.1	59.8	62.5	62.9	64.4



Supplementary figure 2. Trends for Incidence rate per 100 000 population by age, sex and ethnicity, comparing 2007 and 2016.



a. Some data loss occured in 2012 & 2013 during a data migration process

Supplementary figure 3. Standardised HF incidence rate by ethnicity and sex.

Supplementary table 3. Quasi-Poisson regression analysis (i) with ethnicity, age, sex and time; (ii) with age and sex and an interaction term between ethnicity and time

	Model with age, sex, time and ethnicity			**Model with age, sex and interaction term between ethnicity and time**		
Predictors	Incidence Rate Ratio	CI	p	Incidence Rate Ratio	CI	p
Time	0.99	0.985 – 0.996	**0.001**	0.99	0.99 – 1.00	0.086
Time:Chinese				0.99	0.98 – 1.00	0.184
Time:Indian				0.98	0.9646 – 0.9999	**0.049**
Time:Others				1.01	0.99 – 1.02	0.575
Chinese	0.42	0.41 – 0.44	**<0.001**	0.45	0.41 – 0.49	**<0.001**
Indian	1.20	1.14 – 1.26	**<0.001**	1.33	1.18 – 1.48	**<0.001**
Others	0.72	0.68 – 0.76	**<0.001**	0.70	0.62 – 0.79	**<0.001**
Women	0.75	0.72 – 0.77	**<0.001**	0.75	0.72 – 0.77	**<0.001**
Age, in years (ref =20-<25)						
25-<30	1.87	1.42 – 2.49	**<0.001**	1.87	1.42 – 2.49	**<0.001**
30-<35	3.39	2.62 – 4.44	**<0.001**	3.39	2.62 – 4.44	**<0.001**
35-<40	5.95	4.66 – 7.69	**<0.001**	5.95	4.66 – 7.69	**<0.001**
40-<45	10.89	8.63 – 13.95	**<0.001**	10.89	8.63 – 13.94	**<0.001**
45-<50	20.80	16.60 – 26.47	**<0.001**	20.80	16.60 – 26.45	**<0.001**
50-<55	36.83	29.49 – 46.72	**<0.001**	36.82	29.50 – 46.69	**<0.001**
55-<60	61.54	49.36 – 77.97	**<0.001**	61.53	49.37 – 77.92	**<0.001**
60-<65	95.27	76.46 – 120.65	**<0.001**	95.28	76.50 – 120.60	**<0.001**

Supplementary table 3 (continued). Quasi-Poisson regression analysis (i) with ethnicity, age, sex and time; (ii) with age and sex and an interaction term between ethnicity and time

	Model with age, sex, time and ethnicity			**Model with age, sex and interaction term between ethnicity and time**		
Predictors	Incidence Rate Ratio	CI	p	Incidence Rate Ratio	CI	p
65-<70	133.41	107.06 – 168.96	**<0.001**	133.48	107.16 – 168.97	**<0.001**
70-<75	191.29	153.48 – 242.30	**<0.001**	191.31	153.56 – 242.20	**<0.001**
75-<80	240.86	193.03 – 305.37	**<0.001**	240.95	193.19 – 305.32	**<0.001**
80-<85	269.38	215.14 – 342.55	**<0.001**	269.57	215.39 – 342.61	**<0.001**
85+	224.17	178.09 – 286.35	**<0.001**	224.15	178.16 – 286.18	**<0.001**
Observations	1120			1120		
Deviance	7126.760			7086.978		

Chapter 3.3

Trends for Readmission and Mortality after Heart Failure Hospitalization in Malaysia, 2007 to 2016

Yvonne Mei Fong Lim
Su Miin Ong
Stefan Koudstaal
Wen Yea Hwong
Houng Bang Liew
Jeyamalar Rajadurai
Diederick E Grobbee
Folkert W Asselbergs
Sheamini Sivasampu
Ilonca Vaartjes

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ABSTRACT

Background and objectives

Data on population-level outcomes after heart failure (HF) hospitalisation in Asia is sparse. This study aimed to estimate readmission and mortality after hospitalisation among HF patients and examine temporal variation by sex and ethnicity.

Methods

Data for 105,399 patients who had incident HF hospitalisations from 2007 to 2016 were identified from a national discharge database and linked to death registration records. The outcomes assessed here were 30-day readmission, in-hospital, 30-day and one-year all-cause mortality.

Results

Eighteen percent of patients (n=16786) were readmitted within 30 days. Mortality rates were 5.3% (95% confidence interval (CI) 5.1 -5.4%), 11.2% (11.0 –11.4%) and 33.1% (32.9 -33.4%) for in-hospital, 30-day and 1-year mortality after the index admission. Age, sex and ethnicity-adjusted 30-day readmissions increased by 2% per calendar year while in-hospital and 30-day mortality declined by 7% and 4% per year respectively. One-year mortality rates remained constant during the study period. Men were at higher risk of 30-day readmission (adjusted rate ratio (RR) 1.16, 1.13 – 1.20) and one-year mortality (RR 1.17, 1.15 -1.19) than women. Ethnic differences in outcomes were evident. Readmission rates were equally high in Chinese and Indians relative to Malays whereas Others, which mainly comprised Indigenous groups, fared worst for in-hospital and 30-day mortality with RR 1.84 (1.64 -2.07) and 1.3 (1.21 - 1.41) relative to Malays.

Conclusions

Short-term survival was improving across sex and ethnic groups but prognosis at one year after incident HF hospitalisation remained poor. The steady increase in 30-day readmission rates deserves further investigation.

INTRODUCTION

Heart failure (HF) is both a debilitating and costly clinical syndrome, with an expenditure of 346 billion US$ globally.[1] Despite medical advancement in the management of acute coronary syndromes, the five-year survival rates for HF is poorer than most cancers.[2] Nevertheless, cardiac remodelling and progression to HF can be modified by appropriate preventive strategies and timely effective treatments are available. Estimates on the average prognosis of HF at the population level are important for monitoring changes in healthcare delivery. On the individual patient level, knowing the absolute risks of mortality and readmission enables shared decision-making between health providers and patients when making plans for disease management.[3]

As it is in high-income countries, HF is already demonstrated to be a major burden in middle-income countries and this is expected to pose an equal, if not greater financial and morbidity impact as some of these countries are still grappling with a concurrent infectious disease burden.[4] The amount of data published on the epidemiology of HF from these countries is highly disproportionate compared to developed nations. Relying on data extrapolations from high-income countries is inadequate given the differences in healthcare infrastructure, health spending and demographic composition. The Asian HF registry, which included 11 countries in the region, found that one-year mortality rate was 9.6% among registry patients.[5] However, it was also noted that patients enrolled in this registry were mainly treated in academic hospitals with echocardiography expertise and more resources, and hence not necessarily representative of overall hospitalised patients.[5] Recent data from Malaysia, a middle-income country in Southeast Asia, has shown a 39% rise in the absolute number of incident HF hospitalisations from 2007 to 2016 (Su Miin Ong, MSc, unpublished data, 2020). This highlights an urgent need to fill the existing gaps on temporal trends for clinical outcomes, specifically for Asia.[4] Accordingly, our objective was to estimate the short- and medium-term mortality and readmission outcomes after an incident hospitalisation for HF. We then described the temporal variation in these outcomes by sex and ethnicity in this ethnically diverse country.

METHODS

Data sources

We used hospital discharge data from the Health Informatics Centre, Ministry of Health, Malaysia from January 1, 2007 to December 31, 2016. Briefly, the Hospital Discharge Register represents a module within a centralised database known as the Patient Management Information System (*Sistem Maklumat Rawatan Pesakit*). It has been in operation since 1999 with the compilation of aggregated data on inpatient admissions. Then, granular patient records for Ministry of Health (MOH) hospitals became available by gradual increase in hospital participation over the years. Based on data from the Health Informatics Centre, inpatient admissions to public (MOH) hospitals make up to about 83% of HF hospitalisations in the country between 2008 and 2016, with the rest being hospitalisations in private, university and Ministry of Defence hospitals.

We included only data for MOH hospitals to maintain uniformity as data from other hospital types were available for only a later portion of the study. Mortality outcomes were determined via linkage with the National Mortality Database from the National Registration Department and Department of Statistics by matching on the national identification number or passport number for foreign nationalities in combination with date of birth and sex.[6] Overall, death registration in Malaysia has a coverage of more than 90%; there is complete registration in West Malaysia but under-reporting remains in East Malaysia (comprising the states of Sabah and Sarawak).[6–8] Deaths in hospitals were medically-certified by attending physicians or coroners. On the other hand, deaths in the community were certified by informants such as the policemen and medical assistants and these were considered non-medically certified.[9,10] For the reporting of all-cause mortality, we considered all deaths, regardless of whether they were certified by medical personnel whereas for the calculation of cause-specific deaths, only those which were medically-certified were analysed.

Study population

Patients who were aged 20 years and above, who were admitted to a MOH hospital for an incident HF hospitalisation were included. A discharge diagnosis of HF was defined by International Classification for Diseases version 10 (ICD-10) code I50 while

a case was considered an incident hospitalisation if the patient had no admission for HF within the previous two years.[11,12]

Study outcomes and definitions

The main outcomes of this study were trends on 30-day readmission, in-hospital and 30-day mortality rates and lastly, mortality at one-year. In addition, we compared the crude and adjusted differences in these trends by sex and ethnicity. Lastly, we tabulated ICD-10 coded causes of death and readmission.

Deaths from any cause up to one year from date of HF admission were reported for years 2007 to 2016 while readmission data were only available till 2015. A readmission was defined as an admission for any cause within 30 days after discharge from an index HF hospitalisation while in-hospital mortality was defined as death which occurred during the index hospital admission. Information on ICD-10 coded causes of death was available only for seven years, 2007 till 2013. To examine temporal changes in HF admission criteria, we estimated trend changes in the average number of admissions per patient within one year from the index admission.

Information on age at incident HF hospitalisation, sex and ethnicity were available within the Hospital Discharge Register. In 2016, the Malaysian population is comprised of three major ethnic groups, in which there were 68.6% *Bumiputera* (made up of mainly Malays and Indigenous groups), 23.4% Chinese, 7.0% Indians and 1.0% other ethnicities.[13] In the medical records, ethnicity was self-reported and categorised into four groups as follows: (i) Malay, (ii) Chinese, (iii) Indian and (iv) Others which include Peninsular Malaysia Indigenous groups, Sabah and Sarawak Indigenous groups such as Bajau, Kadazan, Murut, Melanau, Kedayan, Iban, Bidayuh as well as non-Malaysian nationalities.[14] Because we anticipate a majority of Others to come from East Malaysia (consisting of two states, Sabah and Sarawak), which is known to have lower hospital densities and healthcare staff per population, and more remote communities than West Malaysia, we sought to determine the relative percentages of ethnicities by these two geographical regions.[15]

Ethical considerations

Ethics approval was obtained from the Medical Research and Ethics Committee, MOH (NMRR-19-1108-47994). A waiver of informed consent was granted as the analyses was done using observational data from routine clinical care. All data

linkages between hospital discharge data and death records were conducted within the data environment of the Health Informatics Centre, MOH and only de-identified aggregated forms of the data were exported.

Statistical methods

We reported crude readmission and mortality rates stratified by age, sex and ethnicity. For trends analyses, we standardised the outcome measures to the 2016 Malaysian population. Multivariable Poisson models was used to quantify the independent effect of age, sex, ethnicity and admission year on the study outcomes. An interaction term between admission year and ethnicity was used to determine if trend changes differed between ethnicities. There was evidence of overdispersion in the data, so quasi-Poisson models were used. A linear model was used to demonstrate statistical significance in the change in number of admissions per patient with time. Only the ethnicity variable had missing data for 0.3% observations and since this was a negligible percentage, they were excluded from the regression analysis. To assess robustness to changes in the definition of incident HF hospitalisation, we compared the estimates from one-year and three-year lookback periods with the main analyses. Statistical significance was set at 0.05. We used the R statistical software version 3.6.1 for all analyses.[16]

RESULTS

Patient characteristics, mortality and readmission rates

Between 2007 and 2016, there were 105 399 incident admissions for HF. The patients had a mean age of 64.1 (standard deviation (SD) 13.3) (Table 1). Fifty-six percent were men and 61% were Malays. Almost all of the Malay (97.8%), Chinese (87.8%) and Indian (99.6%) patients lived in West Malaysia while more than three quarters of Others (78.6%) live in the states of Sabah and Sarawak in East Malaysia.

A total of 16 786 (18.1%; 95% confidence interval (CI) 17.8 -18.3%) patients had a readmission within 30 days of discharge. Mortality rates of hospitalised patients were 5.3% (95% CI 5.1 -5.4%) during inpatient stay, 11.2% (95% CI 11.0 – 11.4%) within 30 days and 33.1% (95% CI 32.9 -33.4%) within a year. The median length of hospital stay (LOS) was 3 days (interquartile range (IQR) 2-5). No

association was found between LOS and in-hospital mortality. (Incidence rate ratio = 1.00, p-value= 0.529, adjusted for age, sex, ethnicity and time trend) Absolute risks for readmission and mortality by age, sex and ethnicity are displayed in Supplementary table 1.

Thirty-day readmission rates were higher in men (19.4%) than women (16.4%). Although there were no apparent differences for inpatient mortality by sex (adjusted p=0.340), mortality rates at 30 days and at one year were greater in men than women (11.4% vs 10.9% and 34.7% vs 31.2%, both adjusted p<0.001) (Table 2). Age at index hospitalisation was a significant determinant of both short- and medium-term (one year) mortality. Patients who were on the extreme ends of the age spectrum, i.e., those aged 20-<25 years and 85 years and older had 2.4- and 1.8-fold increased risk of in-hospital death compared to those who were between 60 and 65 years. For patients who survived past 30 days, the risk of mortality within a year increased gradually from the 30-<35 years age band (adjusted risk ratio 0.85, 95% CI 0.77 -0.94) to the oldest age band of 85 years and above (adjusted risk ratio 1.58, 95%CI 1.49 -1.67) compared to the reference age category (60-<65 years).

By ethnicity, 30-day readmission rates were highest in Indians (19.9%), followed by Chinese (19.5%), Malay (17.9%) and Others (14.5%). For short-term mortality, Others presented with the poorest outcomes: 9.4% for in-hospital mortality and 14.4% for 30-day mortality compared to 4.6% and 10.7% in Malays, the largest ethnic group in Malaysia. This translates to a 1.8-and 1.3-fold increase in risk for mortality relative to Malays when adjusted to age, sex and calendar year. Indian patients, on the other hand, had lower inpatient (3.8%), 30-day (8.4%) and one-year (28.6%) mortality rate than Malays. All ethnic differences in outcome measures remained when estimates were adjusted for age, sex and calendar year.

Table 1. Patient characteristics and clinical outcomes for incident hospitalisations for heart failure

Year	2007-2008		2009-2010		2011-2012		2013-2014		2015-2016	
	n	%	n	%	n	%	n	%	n	%
Age										
Mean (SD)	64.6	13.1	64.3	13.1	64.0	13.3	63.9	13.4	63.7	13.4
Age group										
20-<25	99	0.5	113	0.5	92	0.5	108	0.5	118	0.5
25-<30	147	0.8	171	0.8	184	0.9	186	0.9	214	0.9
30-<35	219	1.2	266	1.3	235	1.2	299	1.4	367	1.5
35-<40	328	1.7	358	1.7	384	2.0	428	2.0	603	2.4
40-<45	575	3.0	707	3.4	641	3.3	740	3.5	920	3.7
45-<50	1123	5.9	1252	5.9	1211	6.2	1244	5.9	1530	6.2
50-<55	1815	9.6	1948	9.2	1898	9.7	1956	9.3	2264	9.1
55-<60	2228	11.8	2599	12.3	2516	12.9	2762	13.1	3177	12.8
60-<65	2603	13.7	3036	14.4	2803	14.4	3190	15.2	3744	15.1
65-<70	2733	14.4	2931	13.9	2666	13.7	2925	13.9	3657	14.7
70-<75	2869	15.2	3184	15.1	2654	13.6	2615	12.4	3046	12.3
75-<80	2106	11.1	2211	10.5	2144	11.0	2391	11.4	2612	10.5
80-<85	1284	6.8	1420	6.7	1276	6.5	1332	6.3	1628	6.6
85+	803	4.2	868	4.1	799	4.1	879	4.2	965	3.9
Sex										
Male	10459	55.2	11743	55.7	10808	55.4	11774	55.9	14082	56.7
Female	8473	44.8	9321	44.3	8695	44.6	9281	44.1	10763	43.3
Geographical region										
West Malaysia	16615	87.8	18891	89.7	17459	89.5	18541	88.1	21989	88.5
East Malaysia	2317	12.2	2173	11.5	2044	10.5	2514	11.9	2856	11.5

Table 1 (continued). Patient characteristics and clinical outcomes for incident hospitalisations for heart failure

Year	2007-2008		2009-2010		2011-2012		2013-2014		2015-2016	
	n	%	n	%	n	%	n	%	n	%
Ethnicity										
Malay	11233	59.3	12732	60.4	12102	62.1	12837	61.0	15242	61.3
Chinese	3522	18.6	3968	18.8	3471	17.8	3764	17.9	4433	17.8
Indian	2182	11.5	2355	11.2	2123	10.9	2284	10.8	2585	10.4
Others	1922	10.2	1793	8.5	1798	9.2	2156	10.2	2585	10.4
Missing	73	0.4	216	1.0	9	0.05	14	0.1	0	0
Length of Stay										
Median (IQR)	3	2-5	3	2-5	3	2-5	3	2-5	3	2-5
Mean (SD)	4.7	12.2	4.5	14.4	4.3	7.0	4.2	7.0	4.1	5.0
Number of admissions per year										
Median (IQR)	1	0-2	1	0-2	1	0-2	1	0-2	1	0-2
Mean (SD)	1.3	2.2	1.4	2.3	1.3	2.1	1.5	2.3	1.6	2.5
Mortality rate										
In-hospital	1309	6.9	1297	6.2	1177	6.0	859	4.1	918	3.7
30-days	2482	13.1	2526	12.0	2285	11.7	2076	9.9	2406	9.7
1-year	6531	34.5	6945	33.0	6299	32.3	6965	33.1	8163	32.9
Readmission rate										
30-days	3144	16.6	3795	18.0	3387	17.4	4039	19.2	2421	19.6†
Total	**18932**		**21064**		**19503**		**21055**		**24845**	

† Data only available for 2015 and its denominator is 12373

Table 2. Multivariable Poisson regression analysis for readmission and mortality rates during hospital stay, 30 days and 1 year

	Readmission		Mortality					
	30-day		In-hospital		30-day		1-year	
	Rate ratio (95% CI)	p-value	Rate ratio (95% CI)	p-value	Rate ratio (95% CI)	p-value	Rate ratio (95% CI)	p-value
Time	1.02 (1.01 – 1.03)	***	0.93 (0.92 – 0.94)	***	0.96 (0.96 – 0.97)	***	1.00 (0.99 – 1.00)	
Sex (ref=Women)								
Men	1.16 (1.13 – 1.20)	***	1.02 (0.97 – 1.08)		1.11 (1.07 – 1.15)	***	1.17 (1.15 – 1.19)	***
Ethnicity (ref=Malay)								
Chinese	1.12 (1.08 – 1.16)	***	1.21 (1.12 – 1.30)	**	1.08 (1.03 – 1.13)	**	0.95 (0.93 – 0.98)	***
Indian	1.12 (1.07 – 1.17)	**	0.82 (0.74 – 0.91)	**	0.80 (0.75 – 0.85)	***	0.87 (0.84 – 0.90)	***
Others	0.81 (0.77 – 0.86)	***	1.91 (1.77 – 2.07)	***	1.30 (1.23 – 1.37)	***	0.96 (0.93 – 0.99)	*
Age (ref=60-<65)								
20-<25	1.14 (0.94 – 1.37)		2.49 (1.88 – 3.22)	***	1.73 (1.40 – 2.11)	***	0.98 (0.85 – 1.12)	
25-<30	1.01 (0.86 – 1.17)		2.62 (2.12 – 3.21)	***	1.75 (1.48 – 2.04)	***	0.99 (0.89 – 1.10)	
30-<35	0.83 (0.72 – 0.95)	**	2 (1.64 – 2.43)	***	1.39 (1.20 – 1.60)	***	0.86 (0.78 – 0.94)	**
35-<40	0.98 (0.88 – 1.08)		1.25 (1.01 – 1.53)	*	1.09 (0.95 – 1.25)		0.83 (0.76 – 0.89)	***
40-<45	0.95 (0.87 – 1.03)		1.15 (0.96 – 1.36)		0.98 (0.88 – 1.10)		0.83 (0.78 – 0.88)	***
45-<50	0.94 (0.88 – 1.01)		0.88 (0.75 – 1.02)		0.84 (0.76 – 0.93)	**	0.82 (0.78 – 0.86)	***
50-<55	0.99 (0.93 – 1.05)		0.85 (0.74 – 0.96)	*	0.82 (0.75 – 0.89)	***	0.87 (0.83 – 0.91)	***
55-<60	0.98 (0.93 – 1.03)		0.93 (0.83 – 1.05)		0.90 (0.83 – 0.97)	**	0.93 (0.89 – 0.96)	***
65-<70	0.97 (0.92 – 1.02)		1.07 (0.96 – 1.20)		1.08 (1.01 – 1.16)	*	1.05 (1.02 – 1.09)	**
70-<75	0.91 (0.87 – 0.96)	**	1.14 (1.02 – 1.27)	*	1.23 (1.15 – 1.31)	***	1.15 (1.11 – 1.20)	***
75-<80	0.86 (0.81 – 0.91)	***	1.26 (1.12 – 1.41)	***	1.34 (1.25 – 1.44)	***	1.24 (1.19 – 1.29)	***
80-<85	0.84 (0.79 – 0.90)	***	1.53 (1.36 – 1.73)	***	1.59 (1.47 – 1.71)	***	1.37 (1.31 – 1.43)	***
85+	0.75 (0.69 – 0.81)	***	1.84 (1.61 – 2.10)	***	1.94 (1.79 – 2.11)	***	1.59 (1.51 – 1.66)	***

*p<0.05, **p<0.01, ***p<0.00

Trends for readmission and mortality

A 17.8% increase in overall readmissions from 16.6% in 2007-2008 to 19.6% in 2015 was observed and this trend remained significant at +2% per calendar year after adjusting for age, sex and ethnicity (p trend <0.001). Figure 1(a) shows that age-standardised trends for 30-day readmission in men were proportionally higher than the rate for women. Although Others had the lowest readmission rates in 2007, its rise with time was the largest compared to the other ethnic groups (Figure 2 (a)). The mean number of hospitalisations per patient within a year has risen slightly from 1.3 in 2007 to 1.6 in 2015 and a modest increase of 0.04 per calendar year was still evident after accounting for age, sex and ethnicity (p trend<0.001).

Overall, in-hospital mortality rates nearly halved from 6.9% (95% CI 6.6 -7.3) in 2007 to 3.7% (95% CI 3.5 -3.9) in 2016 with similar trends for men and women (Figure 1(b)). This declining trend remained after adjustment for age, sex and ethnicity (average -7% per year; p trend <0.001). Improvements in mortality were also evident within 30 days of hospitalisation, seen as a 26% decline from 13.1% (95% CI 12.6 -13.6%) in 2007 to 9.7% (95% CI 9.3 -10.1%) in 2016. Men had consistently higher 30-day mortality rates than women during the study period (Figure 1(c)). Upon full-model adjustment, the average improvement in 30-day mortality was 4% per calendar year (p trend<0.001). By contrast, all-cause mortality in one year remained unchanged throughout the study period (p trend =0.113) with men having almost uniformly higher rates than women (Figure 1(d)).

Despite poorer overall outcomes, Others showed the most pronounced improvements in short-term mortality over time compared to other groups (Figure 2 (b) and (c)). The rates for 30-day mortality between Others and Malays narrowed from 6.2% in 2007 to 3.5% in absolute rate difference in 2016 but this difference was not significant after full model adjustment (p interaction=0.091; Supplementary table 2). With respect to 1-year mortality, only Others showed significant average decline by 1% per year (p interaction =0.021) relative to Malays (Figure 2 (d), Supplementary table2).

Cause of readmission and death

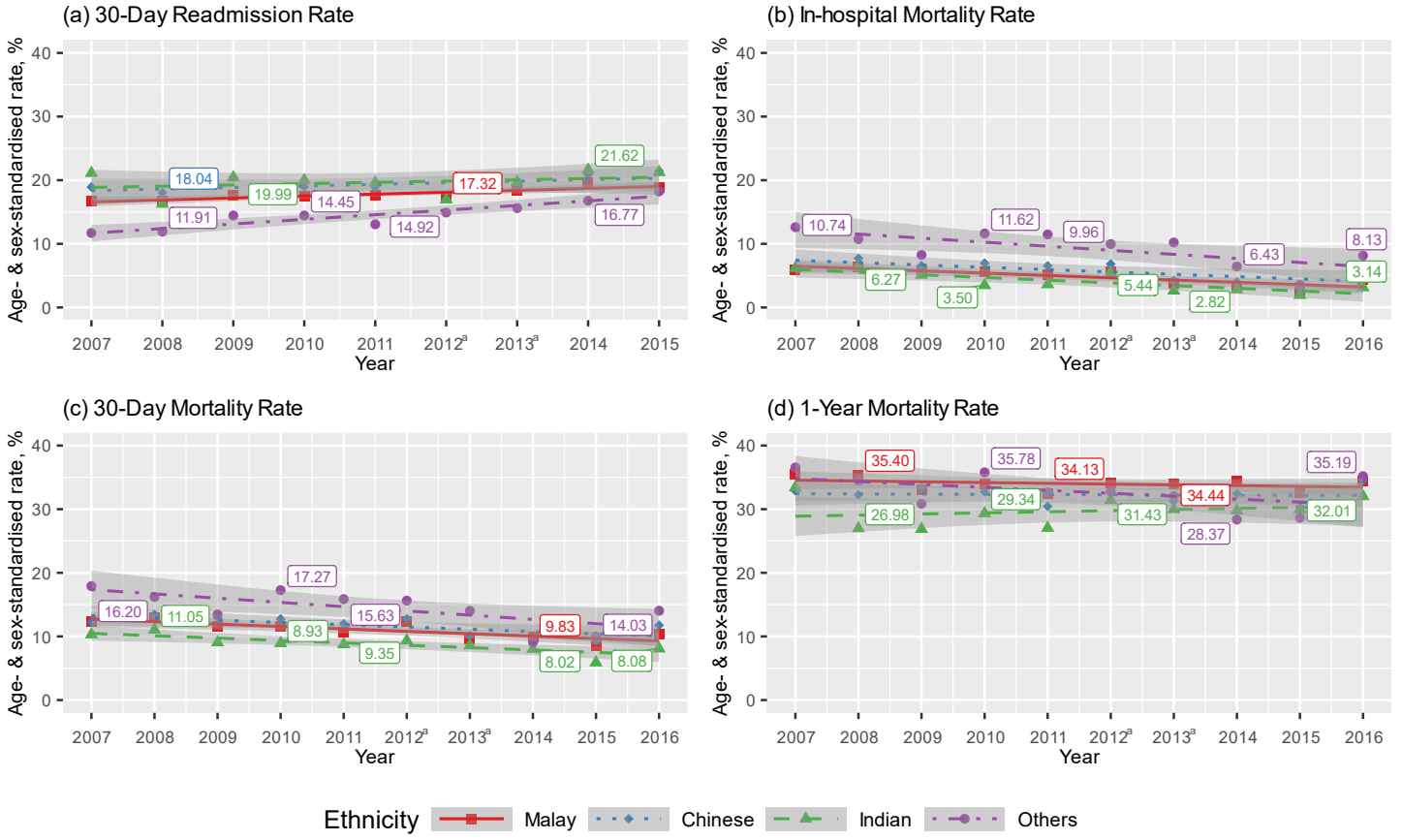
Cardiovascular causes accounted for half of all 30-day readmissions (50.1%) (Figure 3) with HF specifically accounting for 27.7%. Analysis on all medically-certified

deaths found 56% of patients died of cardiovascular causes within a year from index hospitalisation, with the leading cause being HF (21.1%) (Figure 4). Cardiovascular mortality rates have been decreasing by two percent per calendar year, with adjusted p trend=0.001 (Supplementary table 3). Despite this decline, a corresponding increase in non-cardiovascular mortality with time resulted in the unchanged overall rates for one-year mortality and a look into the specific causes between two calendar year periods for 2007- 2008 and 2012-2013 showed that the contribution of infections as a cause of non-cardiovascular deaths has been increasing (Supplementary table 4).

When the definition of incident HF hospitalisation was increased from a two-year to three -year lookback period, the percentage of reduction in false positives were between 1.7 to 3% annually. Nevertheless, the magnitude of outcome rates, trends and statistical significance of regression estimates were similar to the main results, for both the one-year and three-year definitions of incident hospitalisations (Supplementary Tables 5 and 6).

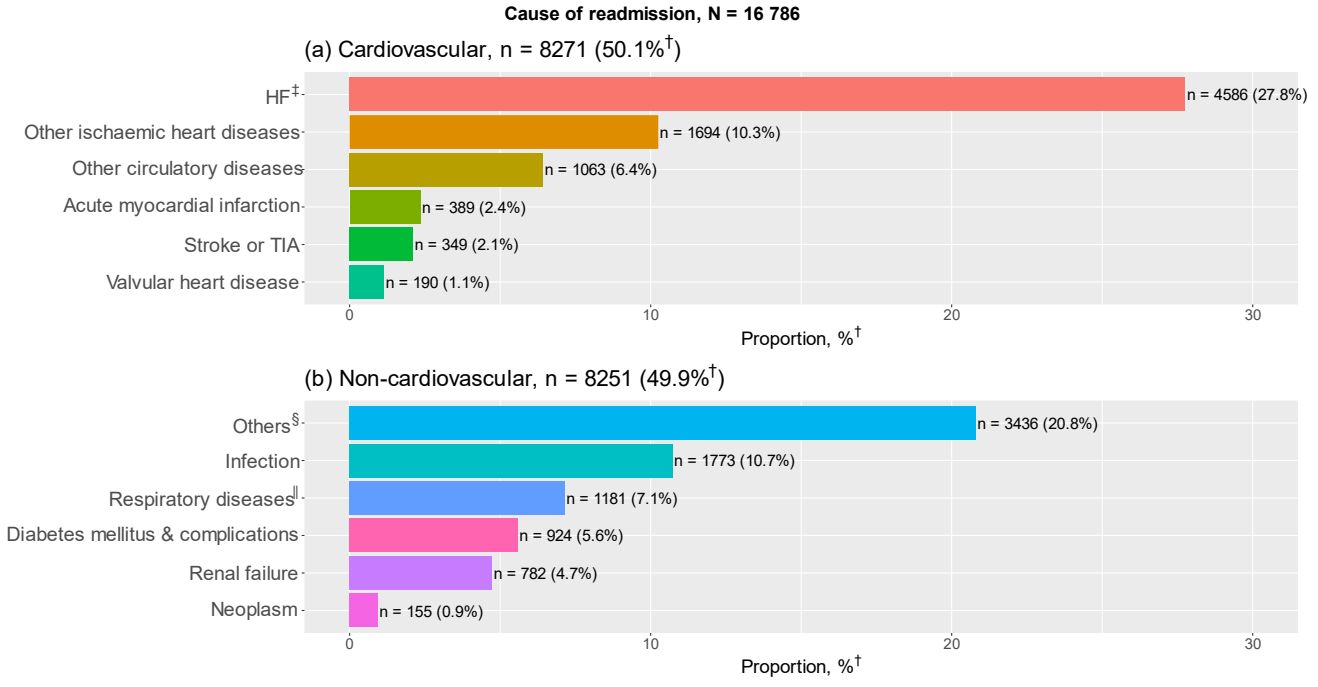
[a] Some data loss occured in 2012 & 2013 during a data migration process

Figure 1. Trends for (a) 30-day readmission, (b) in-hospital, (c) 30-day and (d) one-year all-cause mortality rates by men and women



[a] Some data loss occured in 2012 & 2013 during a data migration process

Figure 2. Trends for (a) 30-day readmission, (b) in-hospital, (c) 30-day and (d) one-year all-cause mortality rates by ethnicity



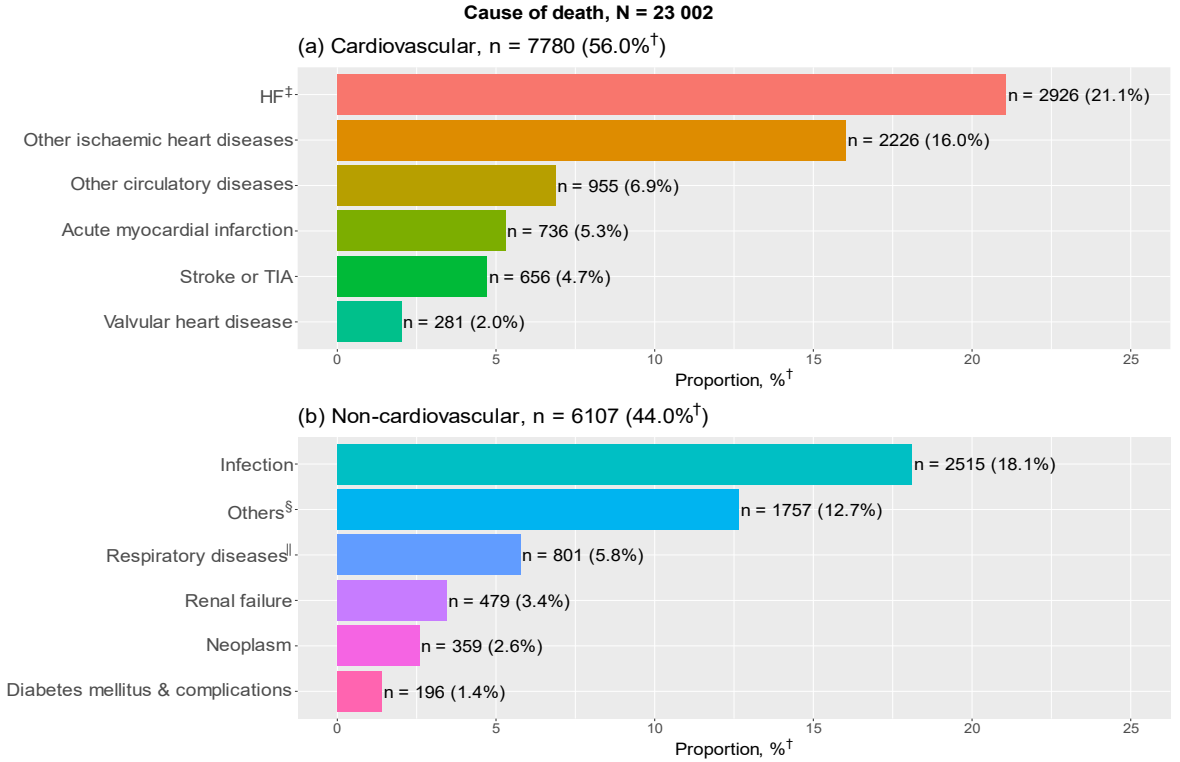
† Percentages were calculated with exclusion of 264 cases of unknown cause of readmission.

‡ Includes cardiomyopathy.

§ Includes gastritis and duodenitis, other disorders of urinary system, other diseases of digestive system, anaemias, poisoning (adverse effect of and underdosing of primarily systemic and haematological agents, not elsewhere classified), shock (not elsewhere classified), hydro-electrolytic disorders, trauma/ injury and etc.

|| Excludes infection

Figure 3. Causes of readmission in 30 days after discharge for index hospital admission from 2007 – 2015



† Percentages were calculated with exclusion of 9115 cases of unknown cause of death.

‡ Includes cardiomyopathy

§ Includes shock (not elsewhere classified), other diseases of digestive system, other disorders of urinary system, chronic nephritic syndrome, hepatic failure (NEC), hydro-electrolytic disorders, trauma/injury and etc.

|| Excludes infection

Figure 4. Causes of death for patients who died within one year after index admission from 2007 – 2013.

DISCUSSION

We present here contemporary crude and age-standardised estimates for mortality and readmission rates among hospitalised HF patients in a middle-income Asian country. Using linked population data, this study has revealed improving trends in short-term mortality following an incident hospitalisation for HF in Malaysia. However, mortality at one year has remained constant while readmissions within thirty days rose steadily during the observation period. We have noted distinct differences in patient outcomes by sex and ethnicity. First, readmission rates were consistently higher in men compared to women and in Chinese and Indians compared to Malay patients. Second, overall short-term mortality outcomes were poorest in Others compared to all other ethnicities while men had slightly worse outcomes than women for 30-day mortality. Third, improvements in survival after HF hospitalisation varied by ethnic groups with Others showing the steepest decline in one-year mortality.

In-hospital mortality after incident HF hospitalisation in Malaysia was higher compared to the 4.1% reported from a HF registry in China.[17] Nevertheless, it is necessary to take into consideration that being enrolled in a registry is associated with better outcomes.[18] Next, we observed a seven percent decline for in-hospital mortality for both men and women. This is in contrast to a rise in Brazil, from 8.3% to 10.8% between 2008 and 2017.[19] Similar to inpatient mortality, the rates of mortality within 30 days was also decreasing, albeit to a smaller extent. No direct comparisons were available for middle-income countries. However, the decline observed here were consistent to those observed in several high-income settings including Western Australia, the Netherlands, and Sweden[20–23]. Several explanations are possible. The observed decline in short-term mortality is partly a reflection of improving population health, as seen with life expectancy increases from 73.7 years in 2008 to 75 years in 2018.[24] Other explanations include earlier identification of cases as a result of rising population health awareness, improved pre-hospital emergency services [25,26] and an increase in the number of medical specialists in the past two decades. MOH hospitals have experienced almost doubling of the number of emergency medicine specialists from 93 to 167 from 2010 to 2013 and a modest increase in the number of cardiologists from 47 to 53 within the same period.[27] There are no known changes in reimbursement practices or implementation of nationwide

quality improvement programs during the study period, therefore we expect the coding of ICD-10 to remain consistent over this duration.

In keeping with earlier and recent studies from Western populations,[28–30] we have also showed that men had higher risks of mortality and readmission than women after accounting for age, ethnicity and time trends. Poorer survival and higher readmission rates in men after HF hospitalisation may be explained by a predominant heart failure with reduced ejection fraction subtype among men and higher prevalence of macrovascular disease, myocardial ischemia and infarction, which underlie the aetiology of HF in this subgroup.[31] Unfortunately, the type of HF and aetiology were not available in the present data.

Amidst the overall improvements in short-term mortality, it is necessary to note that striking ethnic differences exists. Others had poorer outcomes than the rest of the population. This difference was apparent even in the presence of under-reporting of deaths in East Malaysia, from which the majority of Others reside. Hence, we expect the true estimates to be even higher than what was observed. The health status of this subgroup is known to be poorer compared to the general population and is characterised by lower socioeconomic status, shorter life expectancy, undernutrition, insulin resistance and lack of trust in modern medicine.[32] Moreover, accessibility to hospitals remains a challenge for some residents of the interior and remote parts of Sabah and Sarawak and it is also likely that this region has a higher prevalence of rheumatic heart disease which may contribute to poorer outcomes among those hospitalised for HF.[33–35] These findings highlight a need to improve access to healthcare and focus resources to narrow the disparities in short-term mortality particularly in Others. For short-term mortality trends, it is reassuring to observe that the largest disparity in mortality outcomes between Others and Malays have been narrowing. The remaining differences in mortality outcomes between ethnicity represents opportunities for health interventions.

About 1 in 3 patients hospitalised for HF in this study die within a year and this has remained fairly constant during the study period. Mortality at one year is almost 1.5-fold compared to the European Society of Cardiology Long Term Heart Failure registry, reflecting differences in income per capita, health systems and patient characteristics between Malaysia and the European and Mediterranean countries which participated in this registry.[36] Trend-wise, death due to cardiovascular disease has decreased and this could be the result of a higher use of

disease-modifying therapy such as renin-aldosterone angiotensin system inhibitors and beta-blockers in recent years, as reported in several tertiary centres.[37–40] Numerous reports have shown that people of South Asian descent are predisposed to higher risk of ischaemic heart disease compared to the rest of the population.[41] Accordingly, our previous study had also found the highest incidence of HF hospitalisations amongst Indians in the Malaysian population. Interestingly though, when it comes to survival, be it short-term or at one-year, Indians had significantly better survival compared to other ethnic groups. This suggests a stronger influence of environmental and behavioural determinants over genetic influences in HF outcomes. Further investigation into use of HF medications and lifestyle factors by ethnic subgroups would hence be warranted.

Preventing decompensation is an important therapeutic goal after a diagnosis of HF. To our knowledge, there is no published data on 30-day readmission trends after HF hospitalisation among middle-income countries. The steady annual rise in 30-day readmissions that we have found were comparable to those reported in Spain, but in contrast to a two percent reduction among Veteran's Affairs hospital admissions in the United States.[42,43] It is necessary though, to keep in mind that differences in healthcare financing and infrastructure exist between countries of middle- and high-income economies. Lowering admission threshold for HF is a potential reason for this observed rise in readmission rates in this study. 'Differential readmission rates by ethnicity were likely related to socioeconomic status and educational level. This is reflected as higher readmission rates among the Chinese and Indians who largely reside in urban locations, whereas greater access and logistical barriers to care exists among Others.[44] However, narrowing of the gap in readmission rates between Others and the population average suggests that physical access for Others to secondary care is improving over the last decade. The overall increasing trend in 30-day readmissions observed here deserve attention from researchers and policy makers alike because hospitalisations incur the greatest financial costs to HF health expenditures and about a quarter of these readmissions are preventable.[45] Standardised strategies to differentiate the severity of patients who present at the emergency department would be useful for risk stratifying them into those who require admission while the rest may be observed and treated on an outpatient basis. We know that half of these readmissions are due to non-cardiovascular causes; therefore, multi-faceted assessments which address all

comorbidities can be incorporated into early care transition to outpatient clinics, nurse-led home visits and structured telephone monitoring, all of which have shown moderate effectiveness in reducing rehospitalisations.[46,47]

In this study, we estimated the average prognosis after an index hospitalisation for HF using representative data from a large national database. These findings are generalisable to other middle-income countries with similar government-funded health systems and diverse ethnic composition. While most HF hospitalisation data for middle income countries in literature come from urban tertiary centres[4], we have presented here data across a range of hospitals within the public health sector in Malaysia. Unlike patient selection in disease registries, the inclusion of unselected cases of HF hospitalisations here allowed us to make reliable comparisons between sex and ethnic groups.

There were several limitations in this study. Complete data were available for only primary discharge diagnoses; therefore, the absolute number of HF hospitalisations was likely underestimated. Nevertheless, the trend data is unlikely to be affected by this underestimation as the selection criteria used was uniform across time points. We explored the use of secondary discharge diagnoses as proxy for underlying disease severity but found that data completeness was not consistent across time. Therefore, it is difficult to draw conclusions on the severity of patients who were hospitalised for HF. Information on HF subtypes (reduced, preserved and mid-range ejection fraction), medical history, treatments and device therapy were not available in the discharge database and thus, does not allow for correlation of these factors with HF outcomes. While this analysis encompassed an average of 83% of annual HF hospitalisations in Malaysia, it is necessary to point out that we have included only HF patients who were hospitalised in MoH hospitals. Thus, these results are not generalisable to patients treated in the community setting or private hospitals. The 30-day and one-year mortality estimates were slightly underestimated due to incomplete death registration in East Malaysia. Lastly, there were some data losses in 2012 and 2013 and imputations were not feasible in this situation because the exact number of missing records was not known.

To the best of our knowledge, this is one of the first studies to report national, age-standardised estimates for HF prognosis and trends for hospitalised HF patients in the Southeast Asian region. The declining trend and narrowing of ethnic differences for short-term mortality showed that these outcomes are amenable to

targeted interventions. Moreover, the differential HF outcomes by sex and ethnicity seen here highlights the importance of incorporating these determinants into risk predictions models or when calculating likely accrual endpoints in the design of therapeutic studies.

CONCLUSION

Gradual improvements in short-term mortality were seen across sex and ethnicities although relative differences between ethnic subgroups remain apparent. The steady rise in 30-day readmission post-discharge and stagnating 1-year mortality rate raises concern, signalling a need for pro-active efforts from policymakers, physicians and researchers in making HF a priority disease area.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Readmission and mortality risk by age, sex and ethnicity

	30-day readmission n=16753		Mortality					
			In-hospital n=5537		30-day n=11742		1-year n= 34843	
	No. of events	%	No. of events	%	No. of events	%	No. of events	%
Age								
20-<25	98	21.2	65	12.5	92	17.6	161	30.8
25-<30	150	18.9	115	12.9	157	17.6	278	31.2
30-<35	188	15.9	132	9.6	192	14.0	375	27.3
35-<40	334	19.0	119	5.7	223	10.7	545	26.2
40-<45	569	18.4	188	5.3	346	9.7	934	26.3
45-<50	1017	18.3	251	4.0	521	8.2	1644	26.0
50-<55	1676	19.2	380	3.9	793	8.0	2710	27.5
55-<60	2231	19.1	550	4.2	1160	8.8	3893	29.4
60-<65	2614	19.4	685	4.5	1496	9.7	4837	31.5
65-<70	2435	18.7	730	4.9	1580	10.6	4916	33.0
70-<75	2236	17.5	765	5.3	1744	12.2	5166	36.0
75-<80	1672	16.4	669	5.8	1512	13.2	4380	38.3
80-<85	984	16.1	506	7.3	1093	15.8	2919	42.1
85+	549	14.3	382	8.9	833	19.3	2085	48.4
Sex								
Men	10009	19.4	3070	5.2	6706	11.4	20384	34.7
Women	6744	16.4	2467	5.3	5036	10.9	14459	31.2

Supplementary table 1 (continued). Readmission and mortality risk by age, sex and ethnicity

	30-day readmission n=16753		Mortality					
			In-hospital n=5537		30-day n=11742		1-year n= 34843	
	No. of events	%	No. of events	%	No. of events	%	No. of events	%
Ethnicity								
Malay	10120	17.9	2982	4.6	6862	10.7	21573	33.6
Chinese	3307	19.5	1160	6.1	2442	12.7	6642	34.7
Indian	2035	19.9	434	3.8	963	8.4	3292	28.6
Others	1291	14.5	961	9.4	1475	14.4	3336	32.5
Overall								
Rate (95% CI)	18.1	17.8-18.3	5.3	5.1-5.4	11.2	11.0-11.4	33.2	32.9-33.4

Supplementary table 2. Multivariable Poisson regression analysis for 30-day readmission, in-hospital, 30-day and 1-year mortality rates with interaction term between time and ethnicity to determine statistical significance of trend differences by ethnicity

	30-days readmission			**In-hospital mortality**			**30-day mortality**			**1-year mortality**		
	Rate ratio	CI	p	Rate ratio	CI	p	Rate ratio	CI	p	Rate ratio	CI	p
(Intercept)	0.16	0.15 – 0.17	**<0.001**	0.06	0.06 – 0.07	**<0.001**	0.11	0.10 – 0.12	**<0.00**	0.30	0.29 – 0.31	**<0.00**
Time	1.02	1.01 – 1.02	**<0.001**	0.93	0.91 – 0.94	**<0.001**	0.97	0.96 – 0.97	**<0.00**	1.00	0.99 – 1.00	0.231
Time: Chinese	1.00	0.98 – 1.01	0.578	1.01	0.99 – 1.04	0.349	1.00	0.99 – 1.02	0.858	1.00s	0.99 – 1.01	0.738
Time: Indian	1.00	0.98 – 1.02	0.924	0.98	0.94 – 1.01	0.195	0.99	0.97 – 1.02	0.504	1.01	1.00 – 1.03	**0.010**
Time: Others	1.03	1.01 – 1.05	**0.002**	1.00	0.98 – 1.03	0.920	0.98	0.97 – 1.00	0.091	0.99	0.98 – 1.00	**0.021**
Malay	*Reference*											
Chinese	1.14	1.05 – 1.24	**0.002**	1.14	0.98 – 1.31	0.089	1.07	0.97 – 1.18	0.155	0.96	0.91 – 1.01	0.156
Indian	1.11	1.01 – 1.23	**0.038**	0.93	0.75 – 1.14	0.474	0.83	0.73 – 0.96	**0.010**	0.80	0.74 – 0.86	**<0.00**
Others	0.68	0.60 – 0.77	**<0.001**	1.90	1.63 – 2.22	**<0.001**	1.42	1.26 – 1.59	**<0.00**	1.03	0.96 – 1.11	0.369
Female	*Reference*											
Male	1.16	1.13 – 1.19	**<0.001**	1.02	0.97 – 1.08	0.429	1.11	1.07 – 1.15	**<0.00**	1.17	1.15 – 1.19	**<0.00**

Supplementary table 2 (continued). Multivariable Poisson regression analysis for 30-day readmission, in-hospital, 30-day and 1-year mortality rates with interaction term between time and ethnicity to determine statistical significance of trend differences by ethnicity

	30-days readmission			**In-hospital mortality**			**30-days mortality**			**1-year mortality**		
	Rate ratio	CI	p	Rate ratio	CI	p	Rate ratio	CI	p	Rate ratio	CI	p
60-<65	*Reference*											
20-<25	1.14	0.94 – 1.37	0.167	2.49	1.88 – 3.22	**<0.001**	1.73	1.40 – 2.11	**<0.001**	0.98	0.85 – 1.12	0.759
25-<30	1.01	0.86 – 1.17	0.918	2.62	2.12 – 3.21	**<0.001**	1.75	1.48 – 2.04	**<0.001**	0.99	0.89 – 1.10	0.884
30-<35	0.83	0.72 – 0.95	**0.008**	2.00	1.64 – 2.43	**<0.001**	1.39	1.20 – 1.61	**<0.001**	0.86	0.78 – 0.94	**0.002**
35-<40	0.98	0.88 – 1.08	0.654	1.25	1.01 – 1.53	**0.034**	1.09	0.95 – 1.25	0.224	0.83	0.76 – 0.89	**<0.001**
40-<45	0.95	0.87 – 1.03	0.195	1.15	0.96 – 1.36	0.115	0.99	0.88 – 1.10	0.796	0.83	0.78 – 0.88	**<0.001**
45-<50	0.94	0.88 – 1.01	0.078	0.88	0.75 – 1.02	0.089	0.84	0.76 – 0.93	**0.001**	0.82	0.78 – 0.87	**<0.001**
50-<55	0.99	0.93 – 1.05	0.696	0.84	0.74 – 0.96	**0.013**	0.82	0.75 – 0.89	**<0.001**	0.87	0.83 – 0.91	**<0.001**
55-<60	0.98	0.93 – 1.03	0.463	0.93	0.83 – 1.05	0.253	0.90	0.83 – 0.97	**0.005**	0.93	0.90 – 0.96	**<0.001**
65-<70	0.97	0.92 – 1.02	0.215	1.07	0.96 – 1.20	0.220	1.08	1.01 – 1.15	**0.033**	1.05	1.01 – 1.09	**0.006**
70-<75	0.91	0.87 – 0.96	**0.001**	1.14	1.02 – 1.27	**0.020**	1.23	1.15 – 1.31	**<0.001**	1.15	1.12 – 1.20	**<0.001**
75-<80	0.86	0.81 – 0.91	**<0.001**	1.25	1.12 – 1.40	**<0.001**	1.34	1.25 – 1.44	**<0.001**	1.24	1.19 – 1.28	**<0.001**

Supplementary table 2 (continued). Multivariable Poisson regression analysis for 30-day readmission, in-hospital, 30-day and 1-year mortality rates with interaction term between time and ethnicity to determine statistical significance of trend differences by ethnicity

	30-days readmission			**In-hospital mortality**			**30-days mortality**			**1-year mortality**		
	Rate ratio	CI	p	Rate ratio	CI	p	Rate ratio	CI	p	Rate ratio	CI	p
80-<85	0.84	0.79 – 0.90	**<0.001**	1.53	1.35 – 1.73	**<0.001**	1.59	1.47 – 1.71	**<0.001**	1.37	1.31 – 1.43	**<0.001**
85+	0.75	0.68 – 0.81	**<0.001**	1.84	1.61 – 2.10	**<0.001**	1.94	1.79 – 2.11	**<0.001**	1.59	1.52 – 1.66	**<0.001**
Observations	999			1111			1111			1111		
Deviance	894.324			1299.643			1114.947			890.756		

Supplementary table 3. Poisson model for cardiovascular and non-cardiovascular death at one year after index HF admission

	Cardiovascular death			**Non-cardiovascular death**		
Predictors	Rate Ratio	CI	p	Rate Ratio	CI	p
Time	0.98	0.97 – 0.99	**0.001**	1.02	1.01 – 1.03	**0.003**
Female	*Reference*					
Male	1.21	1.16 – 1.26	**<0.001**	1.09	1.04 – 1.14	**0.001**
Malay	*Reference*					
Chinese	1.10	1.04 – 1.16	**0.001**	1.14	1.08 – 1.21	**<0.001**
Indian	1.07	1.00 – 1.14	0.063	1.03	0.95 – 1.11	0.496
Others	1.12	1.04 – 1.20	**0.002**	1.17	1.08 – 1.26	**<0.001**
60-<65	*Reference*					
20-<25	1.56	1.13 – 2.08	**0.005**	1.87	1.38 – 2.48	**<0.001**
25-<30	1.59	1.30 – 1.93	**<0.001**	1.72	1.37 – 2.13	**<0.001**
30-<35	1.15	0.94 – 1.39	0.161	1.47	1.21 – 1.78	**<0.001**
35-<40	1.14	0.97 – 1.34	0.109	1.20	1.00 – 1.43	**0.049**
40-<45	1.06	0.93 – 1.20	0.382	0.93	0.80 – 1.08	0.333
45-<50	0.92	0.82 – 1.02	0.110	0.83	0.74 – 0.94	**0.003**
50-<55	0.95	0.87 – 1.04	0.291	0.88	0.79 – 0.97	**0.011**
55-<60	1.00	0.92 – 1.08	0.905	0.93	0.85 – 1.02	0.146
65-<70	1.02	0.94 – 1.10	0.657	0.96	0.88 – 1.05	0.408
70-<75	1.10	1.01 – 1.18	**0.020**	0.98	0.90 – 1.07	0.672
75-<80	1.08	0.99 – 1.17	0.074	1.08	0.98 – 1.18	0.109
80-<85	1.07	0.97 – 1.18	0.162	1.12	1.01 – 1.24	**0.032**
85+	1.10	0.98 – 1.23	0.109	1.20	1.07 – 1.36	**0.003**
Observations	686			678		
R^2 Nagelkerke	0.277			0.299		

Supplementary table 4. Comparison on causes of death between 2007-2008 and 2012-2013

	2007-2008		2012-2013	
Cause of death	**n**	**%†**	**n**	**%†**
Cardiovascular	**2311**	**60%**	**1955**	**53.5%**
HF + cardiomyopathy	956	24.8%	722	19.8%
Other ischaemic heart diseases	693	18.0%	590	16.1%
Other diseases of the circulatory system	263	6.8%	189	5.2%
Acute myocardial infarction	179	4.6%	210	5.7%
Stroke	146	3.8%	171	4.7%
Valvular heart disease	74	1.9%	73	2.0%
Non-cardiovascular	**1541**	**40%**	**1699**	**46.5%**
Infection	519	13.5%	797	21.8%
Other‡	464	12.0%	488	13.4%
Renal failure	140	3.6%	107	2.9%
Respiratory disease	237	6.2%	189	5.2%
Neoplasm	108	2.8%	87	2.4%
Diabetes mellitus and complications	73	1.9%	31	0.8%
Missing	2679		2254	

†Percentages were calculated based on all known causes of death

‡ Includes shock (not elsewhere classified), other diseases of digestive system, other disorders of urinary system, chronic nephritic syndrome, hepatic failure (NEC), hydro-electrolytic disorders, trauma and other causes

Supplementary table 5. Multivariable Poisson regression analysis for readmission and mortality rates using incident HF hospitalization definition of no prior admission in the past 1 year

	30-day readmission			In-hospital mortality			30-day mortality			1-year mortality		
	Incidence Rate Ratio	CI	p	Incidence Rate Ratio	CI	p	Incidence Rate	CI	p	Incidence Rate	CI	p
Intercept)	0.16	0.15 – 0.17	**<0.001**	0.06	0.05 – 0.06	**<0.001**	0.11	0.10 – 0.11	**<0.001**	0.30	0.29 – 0.31	**<0.001**
Time	1.02	1.01 – 1.03	**<0.001**	0.93	0.92 – 0.93	**<0.001**	0.96	0.96 – 0.97	**<0.001**	1.00	0.99 – 1.00	0.102
Male	1.16	1.13 – 1.20	**<0.001**	1.02	0.96 – 1.08	0.486	1.11	1.07 – 1.15	**<0.001**	1.17	1.15 – 1.19	**<0.001**
Malay	*Reference*											
Chinese	1.11	1.07 – 1.16	**<0.001**	1.21	1.12 – 1.30	**<0.001**	1.08	1.03 – 1.13	**0.001**	0.96	0.93 – 0.98	**<0.001**
Indian	1.10	1.05 – 1.15	**<0.001**	0.82	0.73 – 0.91	**<0.001**	0.81	0.76 – 0.86	**<0.001**	0.88	0.85 – 0.91	**<0.001**
Others	0.82	0.78 – 0.87	**<0.001**	1.92	1.78 – 2.07	**<0.001**	1.30	1.23 – 1.37	**<0.001**	0.96	0.93 – 0.99	**0.007**
60-<65	*Reference*											
20-<25	1.13	0.92 – 1.36	0.228	2.54	1.92 – 3.28	**<0.001**	1.73	1.40 – 2.11	**<0.001**	0.98	0.85 – 1.12	0.770
25-<30	0.99	0.85 – 1.16	0.944	2.62	2.12 – 3.21	**<0.001**	1.74	1.48 – 2.04	**<0.001**	0.98	0.88 – 1.09	0.775
30-<35	0.83	0.72 – 0.96	**0.012**	2.03	1.66 – 2.46	**<0.001**	1.39	1.20 – 1.60	**<0.001**	0.86	0.78 – 0.94	**0.002**

Supplementary table 5 (continued). Multivariable Poisson regression analysis for readmission and mortality rates using incident HF hospitalization definition of no prior admission in the past 1 year

	30-day readmission			In-hospital mortality			30-day mortality			1-year mortality		
	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p
35-<40	0.95	0.85 – 1.06	0.403	1.31	1.07 – 1.59	**0.008**	1.11	0.97 – 1.26	0.138	0.83	0.77 – 0.89	**<0.001**
40-<45	0.94	0.86 – 1.02	0.148	1.17	0.98 – 1.38	0.071	0.99	0.88 – 1.10	0.840	0.83	0.78 – 0.88	**<0.001**
45-<50	0.94	0.88 – 1.01	0.072	0.89	0.76 – 1.03	0.126	0.84	0.77 – 0.93	**<0.001**	0.83	0.79 – 0.87	**<0.001**
50-<55	1.00	0.94 – 1.06	0.996	0.87	0.76 – 0.99	**0.032**	0.83	0.76 – 0.90	**<0.001**	0.87	0.84 – 0.91	**<0.001**
55-<60	0.99	0.93 – 1.04	0.592	0.96	0.85 – 1.08	0.485	0.91	0.84 – 0.98	**0.010**	0.94	0.90 – 0.97	**0.001**
65-<70	0.98	0.93 – 1.03	0.467	1.09	0.98 – 1.21	0.130	1.08	1.01 – 1.16	**0.022**	1.05	1.02 – 1.09	**0.004**
70-<75	0.92	0.87 – 0.97	**0.003**	1.15	1.03 – 1.28	**0.013**	1.22	1.14 – 1.30	**<0.001**	1.15	1.11 – 1.19	**<0.001**
75-<80	0.87	0.82 – 0.92	**<0.001**	1.27	1.14 – 1.42	**<0.001**	1.34	1.25 – 1.44	**<0.001**	1.23	1.19 – 1.28	**<0.001**
80-<85	0.86	0.80 – 0.92	**<0.001**	1.54	1.36 – 1.73	**<0.001**	1.58	1.46 – 1.70	**<0.001**	1.36	1.31 – 1.42	**<0.001**
85+	0.75	0.68 – 0.82	**<0.001**	1.85	1.62 – 2.10	**<0.001**	1.93	1.78 – 2.10	**<0.001**	1.57	1.50 – 1.64	**<0.001**

Supplementary table 6. Multivariable Poisson regression analysis for readmission and mortality rates using incident HF hospitalisation definition of no prior admission in the past 3 years

	30-day readmission			**In-hospital mortality**			**30-day mortality**			**1-year mortality**		
	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p
Intercep	0.16	0.15 – 0.1	**<0.00**	0.06	0.05 – 0.0	**<0.00**	0.11	0.10 – 0.1	**<0.00**	0.29	0.28 – 0.3	**<0.00**
Time	1.02	1.01 – 1.0	**<0.00**	0.92	0.91 – 0.9	**<0.00**	0.96	0.96 – 0.9	**<0.00**	1.00	1.00 – 1.0	0.969
Female	*Reference*											
Male	1.16	1.13 – 1.2	**<0.00**	1.02	0.96 – 1.0	0.576	1.12	1.08 – 1.1	**<0.00**	1.17	1.15 – 1.1	**<0.00**
Malay	*Reference*											
Chinese	1.11	1.07 – 1.1	**<0.00**	1.23	1.14 – 1.3	**<0.00**	1.10	1.04 – 1.1	**<0.00**	0.96	0.93 – 0.9	**0.001**
Indian	1.10	1.05 – 1.1	**<0.00**	0.80	0.71 – 0.9	**<0.00**	0.80	0.74 – 0.8	**<0.00**	0.86	0.83 – 0.8	**<0.00**
Others	0.81	0.77 – 0.8	**<0.00**	1.91	1.76 – 2.0	**<0.00**	1.28	1.21 – 1.3	**<0.00**	0.94	0.91 – 0.9	**0.001**
60-<65	*Reference*											
20-<25	1.16	0.95 – 1.4	0.143	2.50	1.85 – 3.2	**<0.00**	1.78	1.42 – 2.1	**<0.00**	1.01	0.87 – 1.1	0.914
25-<30	1.00	0.85 – 1.1	0.967	2.72	2.18 – 3.3	**<0.00**	1.83	1.55 – 2.1	**<0.00**	1.03	0.92 – 1.1	0.612

Supplementary table 6 (continued). Multivariable Poisson regression analysis for readmission and mortality rates using incident HF hospitalisation definition of no prior admission in the past 3 years

				In-hospital mortality			30-day mortality			1-year mortality		
	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p	Incidence rate ratio	CI	p
30-<35	0.84	0.73 – 0.9	**0.020**	2.01	1.63 – 2.4	**<0.00**	1.39	1.19 – 1.6	**<0.00**	0.87	0.78 – 0.9	**0.004**
35-<40	0.97	0.87 – 1.0	0.607	1.22	0.97 – 1.5	0.083	1.08	0.93 – 1.2	0.299	0.82	0.75 – 0.8	**<0.00**
40-<45	0.94	0.86 – 1.0	0.166	1.14	0.95 – 1.3	0.166	0.98	0.86 – 1.1	0.697	0.83	0.77 – 0.8	**<0.00**
45-<50	0.95	0.88 – 1.0	0.126	0.88	0.75 – 1.0	0.121	0.84	0.76 – 0.9	**0.001**	0.83	0.79 – 0.8	**<0.00**
50-<55	0.99	0.94 – 1.0	0.839	0.83	0.72 – 0.9	**0.012**	0.81	0.74 – 0.8	**<0.00**	0.87	0.83 – 0.9	**<0.00**
55-<60	0.98	0.93 – 1.0	0.521	0.94	0.83 – 1.0	0.366	0.90	0.83 – 0.9	**0.013**	0.93	0.89 – 0.9	**<0.00**
65-<70	0.97	0.92 – 1.0	0.237	1.09	0.97 – 1.2	0.161	1.08	1.00 – 1.1	**0.042**	1.05	1.01 – 1.0	**0.017**
70-<75	0.92	0.87 – 0.9	**0.004**	1.14	1.01 – 1.2	**0.028**	1.23	1.14 – 1.3	**<0.00**	1.15	1.11 – 1.2	**<0.00**
75-<80	0.87	0.82 – 0.9	**<0.00**	1.23	1.09 – 1.3	**0.001**	1.32	1.22 – 1.4	**<0.00**	1.24	1.19 – 1.2	**<0.00**
80-<85	0.85	0.79 – 0.9	**<0.00**	1.55	1.36 – 1.7	**<0.00**	1.59	1.46 – 1.7	**<0.00**	1.37	1.31 – 1.4	**<0.00**
85+	0.75	0.68 – 0.8	**<0.00**	1.83	1.58 – 2.1	**<0.00**	1.93	1.76 – 2.1	**<0.00**	1.59	1.51 – 1.6	**<0.00**

4

General Discussion

DISCUSSION

Since the success of the first heart failure therapeutic trial more than 30 years ago, survival of patients with HF have improved substantially. This improvement applies only to the HFrEF phenotype, encompassing about 50% and 60% of hospitalized and ambulatory HF patients, respectively.[1–3] At least six therapeutic classes of proven clinical benefit by mortality and morbidity reductions and symptom relief are available for the treatment of chronic HFrEF. These are: (i) angiotensin-converting enzyme inhibitors (ACEi) , (ii) angiotensin-II receptor blockers (ARB), (iii) beta-blockers (BB), (iv) mineralocorticoid receptor antagonists (MRA), (v) neprilysin inhibitor (ARNI, sacubitril-valsartan) and (vi) sodium-glucose co-transporter 2 inhibitor (SGLT2i).[4] Other treatments such as digoxin, ivabradine and vericiguat are available for specific subgroups and these work mainly by reducing risk of HF hospitalization.[5–7] Taken together, about 73% reduction in mortality is anticipated with quadruple (BB, MRA, ARNI and SGLT2i) therapy.[8]

In practice, data from high income regions showed that the largest decline in mortality for HF occurred between 1980 and 2000.[9] This coincides with the introduction and uptake of renin-angiotensin system (RAS) antagonists for HF.[10] However, improvements in mortality in HF patients subsequently slowed, levelled and more recently, showed a reversed upward trajectory from 2015[10–12] signaling that incremental benefits from therapeutic development in HFrEF have yet to translate into population survival gains of comparable magnitude in the recent two decades. These stalling mortality rates are not isolated to Europe and North America but also observed in middle-income regions in Asia.[13,14]

Part of the reluctance or dilemma to use all proven medical treatment for HFrEF and up-titrate to target doses can be attributed to differences in titration strategies and populations seen in the explanatory trials versus those in routine care. The gap in data on safety and efficacy in under-represented subgroups, particularly older persons, women, individuals with comorbidities and organ dysfunction leads to hesitation to apply a one-size-fit-all approach to population in which frailty is common. When it comes to generalizability of HFrEF clinical evidence, the ultimate goal would be to encompass the full spectrum of patients who will receive the treatment post regulatory approval. In this chapter, we will discuss the present state

of HFrEF trial generalizability and the future path toward generalizable clinical evidence.

Quantitative representation by key demographic groups

The most pressing concern in HFrEF efficacy trial generalizability lies in persistent under-enrolment of females, which stands between 21% and 27%, [15–18] though females make up to 41% and 47% of hospitalized and ambulatory HFrEF patient cohorts.[19,20] In light of clear epidemiological differences between sexes, from predisposing factors to pathophysiology, diagnostic features, treatment practices, pharmaco-kinetics and -dynamics and clinical outcomes[13,21–25], the assumption that male-driven efficacy results can be safely extrapolated to female HF patients no longer holds. In fact, a recent meta-analysis on sex-stratified efficacy of HFrEF trials found neutral pooled effects in females for renin-angiotensin system (RAS) antagonists and beta-blockers, indicating that overall positive treatment effects reflect results seen only in male participants.[26] In a post-hoc comparison between HFrEF trials and registry, we demonstrated that men in the trials have a-third higher residual cardiovascular risk than trial women. Furthermore, standard target doses in guidelines for HFrEF are being called into question as females from Asian and European cohorts were found to reach maximal treatment benefits for ACE-inhibitors / ARBs and beta-blockers with just half the recommended doses.[27] Thus, existing practices of reporting subgroup analyses by sex or post-hoc meta-analyses are no longer sufficient in mitigating generalizability concerns if females continue to make up only a quarter of participants. Closing of gaps in evidence among females requires proactive modernization of HF clinical trials, considering alternatives including stratified purposive sampling[28] and built-in mechanisms to increase enrolment of females.

The next important subgroup to represent in efficacy trials is older patients. In HFrEF trials, mean participant age continue to remain at 65 years, [15,16] 10 years younger than the general HFrEF population in Western Europe and Northern America (72-74 years).[29–31] It is necessary to note that the gap in trial representativeness depends on the reference population in question. Comparatively, the average age in the trials is similar when compared to HFrEF patients from Asia, where onset of HF is earlier.[13,32] While age is an important prognostic indicator, underrepresentation of older patients is tied to under-representation based on other characteristics, for

instance sex; females with HF tend to be older and so are patients with multiple comorbidities. With the exception of conducting trials specifically in older patients, such as the SENIORs trial for beta-blockers in ≥70-year-olds,[33] designing phase III efficacy trials with sufficient representation for every age stratum greatly increases costs and complexity. When efforts to ensure equitable female enrolment and justified comorbidity-based exclusions are in place, age distribution of enrolled patients could be expected to accordingly shift to cover a greater proportion of older patients.

Racial/ ethnic variations in response to HFrEF treatment are established[34]; exemplified by the first race-based US Food and Drug Administration (FDA) approval of hydralazine-isosorbide dinitrate combination, which favorable response was elicited solely among Black patients.[35,36] Further, pooled subgroup results from DAPA-HF and EMPEROR-reduced trials for SGLT2 inhibitors in HFrEF revealed attenuated pooled hazard ratios in Whites compared to Black and Asian subgroups.[37] However, compared to sex and age, generalizability of evidence in HFrEF based on race/ ethnicity is the least understood. At present, estimation of generalizability by race/ ethnicity is hindered by sparse reporting of race/ethnicity data in trials. Only half had information on race/ethnicity[15] whereas observational data are typically restricted to individual countries due to law and privacy issues, and is scarce for low-income regions. Inter-national registries such as ESC heart failure long-term registry, ASIAN heart failure registry and INTER-CHF have successfully bridged HF patients across national borders within select continents. These examples therefore set the stage for extension to future cross-continental registries to allow understanding of the HF landscape across the globe.[38–40]

Understanding racial/ethnic diversity in HFrEF trials depends very much on the reference geographical location and its racial/ethnic composition. Given that majority of trials are weighted towards North American and Western European patients, an example on assessing racial representativeness of the ASCEND-HF trial on nesiritide was possible with the Get With The Guidelines-Heart Failure registry for U.S. hospitalized HF patients.[41] Based on comparison with the registry, study investigators found adequate representation of Black patients in the trial though registry black patients experienced worse outcomes compared to their trial equivalents.[41] Clinical trials conducted in the U.S. are usually inclusive of racial/ethnic groups.[42] Over time, globalization of contemporary HF trials has successfully

increased participation of Asian individuals from 1% in 2001-2004 to 20% in 2013-2016 though trial participation from Black and Hispanic patients from other regions either remained stagnant or declined.[15] In this aspect, expansion of sites to Sub-Saharan Africa, Latin America and other Asia Pacific regions would contribute to racially/ethnically more generalizable HF trials.

Assessing generalizability based on race/ethnicity is also complicated by variation in nomenclature and classification of racial/ethnic groups between populations. For instance, the Malaysian population is broadly classified as Asians or South-East Asians in clinical studies[43], but in itself can be subclassified to its Malay ethnic majority (51%) and Chinese, Indian, Indigenous group minorities and non-citizens.[44] Within what is regarded a homogenous population of South-East Asians, we observed inter-ethnic differences in incident heart failure hospitalizations, whereby Indians had a 20% higher risk compared to the nation's major ethnic group. Similarly for HF outcomes, we report disparities between ethnicities within a setting that has tax-funded universal health access. Others, consisting mainly Indigenous groups, experience markedly higher inpatient mortality (1.9-fold higher) and 30-day mortality (1.3-fold higher) compared to Malays. On the contrary, Indians had 20% and 13% lower risk of 30-day and 1-year mortality. These observed ethnic disparities for HF remained after adjustment for age, sex and year of admission, highlighting that racial/ethnic information in trials need to go beyond broad racial groups such as Asian/non-Asian or Hispanic/non-Hispanic[42] and include specific countries, origins and ethnicities for disentangling heterogeneity of risks and therapeutic responses.

Qualitative representation on HF severity, prevalent comorbidities and background heart failure therapy

By estimating eligibility on inclusion and exclusion criteria, we showed that enrolment for HFrEF trials have become stricter by more than two-fold in the past 20 years. One of the reasons to this change is growing numbers of exclusion criteria per trial as part of strategies to maximize validity of causal estimates, termed broadly as practical (efficacy) enrichment.[45–47] Although opinions on the value of representation in study samples is non-unanimous,[48] it is clear that extensive lists of exclusion cause greater therapeutic uncertainty for underrepresented patients which becomes more problematic when it concerns a significant fraction of the treated population.

Therefore, re-examining eligibility criteria of HFrEF trials in these times of rising trends of HF comorbidities has its merits.[49]

Non-cardiovascular comorbidities most often excluded from HFrEF trials were chronic kidney disease (CKD) (55% of trials), COPD or asthma (28%), cancer (25%), liver disease (21%), anaemia or iron deficiency (17%), neurological disorder including dementia, thyroid disorder, depression and so on. Majority of these conditions are clustered with HFrEF.[50,51] Excluding major comorbidities such as anemia and COPD or asthma would mean that more than one-third and one-fifth of HFrEF registry patients are ineligible. Rather than solely presenting with competing risks, existing literature indicate that concomitant CKD and anaemia or iron deficiency in HF do contribute independent risks to cardiovascular progression.[52–54] Therefore, phase III HFrEF trials should generally be inclusive of patients with CKD, anaemia or iron deficiency and COPD unless justified by unacceptable safety risks such as advanced disease stages, contraindication or involvement with drug metabolism or excretion. Further research on the relative competing risks from each prevalent comorbid conditions in HF will enable data-driven eligibility criteria decisions, balancing between impact on primary endpoint detection and gains in trial accrual rates.

To identify patients with higher event rates for cardiovascular outcomes, contemporary trials in HFrEF utilize prognostic enrichment markers or characteristics. A quarter of RCTs for HFrEF enriched for higher CV risk from a recent HF hospitalization and a-fifth applied minimum threshold criterion N-terminal pro b-type natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP). It is FDA-accepted clinical trial practice to establish efficacy in narrower subsets of high-risk patients follow with larger studies in lower risk patients.[45] However, follow-up trials of patients with the same HF phenotype but without the prognostic marker or pragmatic trials are rarely conducted.[55] Moreover, the absence of a standardized way for practicing clinicians to prospectively identify patients with greater likelihood to respond to treatment only adds to hesitation in adopting newer treatments. To navigate the issue of restrictive prognostically enriched trial populations, adaptive designs that include a subset of patients who do not meet the enrichment criterion is useful, particularly when sensitivity of a prognostic marker is not fully understood.[56] Results for the full spectrum of patients, whether marker positive and negative, can then be reported as secondary efficacy outcomes.[56]

Next, contemporary trials often require optimization of background HF medical and device therapy to demonstrate incremental benefit of new treatments. We showed that half of HFrEF trials registered in Clinicaltrials.gov required patients to be on 'standard' or 'optimal' medical therapy of which a quarter specifically mentioned RAS antagonists and beta-blockers and ten percent required background MRA regimen. The fact that majority do not explicitly define optimal therapy in the inclusion criterion signals the difficulty of identifying a single standard treatment. Doses aside, RAS antagonists and BB are widely implemented in practice with almost 90% of patients who are treated with double therapy.[38] However, optimization to target doses has been exceedingly challenging, illustrated by futility of the GUIDE-IT trial for HF treatment intensification.[57] Despite a protocol-driven approach by experienced HF cardiologists, only 15.5% of patients were optimized on GDMTs at 6 months.[57] Reasons for not adjusting therapy include clinical stability and maximally tolerated therapy achieved, which raises the question of whether present GDMT goals were unrealistic to implement.[57] In view of variations in availability, affordability and tolerability between populations, it is therefore time to re-think whether mandating background treatment, for instance a four-drug class approach[58] is overly idealistic;[59] especially when uptake of newer therapies such as sacubitril/valsartan and SGLT2i have been slow.[60] Rather than restricting eligibility based on an ambiguous criterion of 'standard background GDMT', trial designers can measure the extent of background treatment on a scale such as one defined by the Heart Failure Collaboratory[58] and model this information in the analysis as a probability for the outcome or trial membership or both.[28]

Data framework and analytic methods: the means to reach generalizable evidence

Large collaborative consortia such as the Innovative Medicines Initiative BigData@Heart consortium facilitated sharing of individual-level HFrEF clinical trial data across multiple industry partners, setting in motion collaborations historically impeded by conflicts of commercial interest.[61–63] Within this partnership, researchers from an academic university, UMC Utrecht formed the analytic center for pooled individual-level analyses of data from six pharmaceutical and academic partners.

Target population data can be derived from patient registries, electronic health records (EHR) and administrative claims or billing databases. HF registries including

CHECK-HF in the Netherlands, Swedish heart failure registry and BIOSTAT-CHF and ASIAN-HF represent quality sources of patient data that were specifically designed for HF research. Registries have detailed and structured information on HF severity measures, medical history, electrocardiogram, echocardiography, clinical and laboratory measurements which were important for case-mix adjustment, given the complexity and heterogeneity of patients with this condition.[64–67] Although international registries allow us to understand cross-border practice, it is necessary to recognize that patient and site selection do take place. Study sites in registries are typically academic centres or hospitals and investigators involved usually have specific interest in heart failure.[68] On the other hand, EHRs offer broader reflection of everyday patients but lacks uniformity in data on disease severity and requires substantial effort to pre-process and structure free-text clinical notes into scalable, computable formats. Currently, disease-specific registries and electronic records complement one another as they each bring unique advantages in terms of data completeness and uniformity and spectrum of HFrEF severity.

To leverage on growing quantities and dimensions of biomedical data, large-scale data pooling can be done by combining data from different organizations into a single large data set and analyzing by individual-level meta-analysis (ILMA). Although this approach offers convenience for analytics, it is typically not possible owing to ethical and legal constraints on third-party data transfer.[69] For this reason, a data federation framework or decentralized model is proposed to link multiple disparate data repositories across institutional and cross-jurisdictional boundaries to a central analytic computer.[70] This way data shall remain geographically localized but accessible by data queries. Federated data systems require agreed and shared technological infrastructure, data and metadata interoperability, legal and governance policies and an example is CanDIG, a Canadian federated data system for research on genomic data.[71] Mapping of terminologies to a common data model for cardiovascular research was also undertaken by BigData@Heart consortium partners. While this is in progress, data providers in the consortium agreed to first share data via an approach that minimally aggregates data to preserve some granularity while assuring privacy. For small datasets, an issue with low table cell counts of between one and three patients poses a risk of identifying patients. We circumvented this by assigning a central number of two[72] and tested the extent of information loss from aggregation. From this, we demonstrated insignificant loss of

information for the variables tested: age, creatinine and haemoglobin, whereby cumulative distribution curves of the aggregated data stayed within the 95% confidence interval bands of the original variables. (Schröder et al. – manuscript submitted to BigData)

The federated approach to data analysis involves passing lines of analytic codes and summary statistics or regression estimates between data owners and an analytical centre.[69] However, present methods for modified ILMA only permits combining studies of similar data or populations[69] and were not designed for covariate-adjusted comparative analysis of two or more study populations. To estimate clinical trial generalizability, we intended to compare pooled trial data against registry data while simultaneously accounting for confounding on the individual-level within each data set. Since conventional survival regressions could not be used, we estimated a standardized mortality ratio (SMR) of observed-to-expected event rates for each trial. The expected mortality rate for each trial were calculated based on a predictive model fitted within the registry, which stores data on probability of mortality as a function of age, sex, body mass index, history of diabetes or COPD, LVEF, NYHA class, systolic blood pressure, serum creatinine and smoking status.[16,73] If the mortality rate within a trial equals the registry upon prognostic factor adjustment, then the SMR would be 1, i.e. observed mortality=expected mortality. The SMRs were then combined by meta-analysis to obtain a pooled, confounder-adjusted estimate of events in trials relative to registry patients. We have proposed here a straightforward approach to an analytic challenge in federated data analysis that was done sequentially by study partners at the request of the analytic centre. In an established federated database system, a model can be updated directly from the analytic centre, allowing flexibility in the process and timely results. To address gaps in analytic capability, adapted methods for generalized linear models are currently being developed and proposed for federated data sets.[74,75]

Future perspectives

Phase III trials for HF are among the costliest of cardiovascular trials; ranging from USD 142 million for a hypothetical 14500-patient trial in 2001 to an estimated USD 347 million in the 8442-patient trial for sacubitril-valsartan in 2017.[76–78] A recurring theme contributing to more than two-fold rise in drug development costs for HF

therapeutics is increasing trial management complexity for which strategies such as simplifying patient enrolment effort, reducing variables on case report forms (averaging at 165 pages in 2012) and frequency of monitoring and patient visits have been proposed.[47,76,79]

The notion of expanding generalizability is often associated with larger trials. However, relaxing trial entry criteria also presents advantages in reduced recruitment complexity, accelerated participant enrolment and reduction in recruitment cost per patient of up to 21%.[80] In a cost analysis of phase III cardiovascular trials, Eisenstein and colleagues demonstrated 40% total cost savings with fewer CRF pages, monitoring and site visits while maintaining the same number of patients and sites.[76] Concerns with increased patient heterogeneity, non-cardiovascular competing risks or low event rates can be understood and mitigated by data-driven optimization at the pre-design stage. Clinical trial simulation is an established practice among pharmaceutical companies to traditionally model design variability such as dose, schedule, study size and risk of protocol deviations.[81,82] Existing expertise can be used to simulate What-if scenarios of more inclusive enrolment criteria on expected hazard ratios, trial accrual and follow-up duration. Examples are seen in cancer trials whereby change in efficacy endpoints were simulated in a trial setting with and without addition of patients with low performance status.[83] Additionally, machine learning approaches provide opportunities for optimizing balance between eligibility criteria, outcome event rate and projected generalizability of results.

The reality remains that clinical evidence that has low generalizability impacts implementation down the pipeline be it from a regulatory, practicing clinician, payer or patient perspective.[47] The American Society for Clinical Oncology, together with Friends of Cancer Research and FDA issued working group recommendations focusing on broadening four criteria topics that commonly lead to exclusion in cancer trials: brain metastases, minimum participant age (to include pediatric cohorts), HIV infection and organ dysfunction and prior or concurrent malignancy.[84,85] Though primarily focused on the US setting[86], public-private collaborations like the Heart Failure Collaboratory[87] play influential roles to bring together relevant stakeholders in open discussions and consensus for more inclusionary trial enrolment practices. A key long-term goal of the Collaboratory is representative populations; with specific objectives comprising standards for

representative populations to trials based on HF epidemiology and novel methods for recruitment of underrepresented patient groups.[86,87]

A widely accepted solution to generalizable clinical evidence is pragmatic trials but this option can be unattractive when returns on investment are uncertain, particularly to industry sponsors.[55] Perhaps more stands to be gained by embedding pragmatic elements earlier in phase III explanatory HF trials.[55,88] Multi-national HF registries represent promising platforms for cost-efficient and more inclusive patient identification and screening for double-blind explanatory trials. A pioneering example is the DAPA-MI trial for myocardial infarction, the first indication-seeking registry-based RCT which enrolled patients from cardiovascular disease registries in Sweden and the UK. On a similar note, adaptive trial designs have been proposed in a guidance for industry by the FDA in situations where a drug is expected to have larger effects in a targeted subpopulation, whether by demography or pathophysiology.[89] Rather than an all-or-none rule, a trial may enroll populations with and without the characteristic of interest up till an interim analysis period. Then, a decision can be made based on pre-specified terms whether to continue with the overall study population or restrict to the targeted group.[56] An advantage of such adaptive enrichment designs is that data on the intervention will be available for the non-targeted or complementary subpopulation.[89]

Lastly, generalizability metrics provide a quantifiable means to benchmark representativeness of trial samples against the intended target population as well as infer expected treatment effects at a population level. Numerous methods have been proposed for calculating eligibility based on eligibility criteria, assessing overlap between study samples and target population with regard to demographic and prognostic characteristics and statistical extrapolation of effects from narrow study samples to broader populations by applying weights derived from propensity scores to the RCT sample to mimic the target population and estimate population average treatment effects.[90–96] Pre-requisites for the abovementioned methods include access to individual-level data to both RCTs and the target population with comparable measure and sufficient overlap of covariates.[28]

It is exciting and challenging times for therapeutic development in heart failure now that generalizability and representation of trial populations is brought into focus. The path forward requires multi-faceted and -stakeholder strategies, both working in tandem.

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Appendices

SUMMARY

Medical and technological advances have improved patient care in heart failure, particularly in a subtype known as heart failure with reduced ejection fraction (HFrEF). The evidence which guides treatment standards come from carefully designed and executed clinical trials. A series of successful clinical trials since the 1990s have provided us with at least five drug categories that are effective in reducing deaths and other medications which reduce symptoms and hospitalization in selected patients. On a global scale, this signals availability of effective treatment for over 64 million people living with heart failure. If most of these patients were adequately treated with these medications, we expect to witness progressive gains in population survival. This observation holds true for a period between the 1990s and 2000s, where deaths among people with heart failure declined. However, mortality trends thereafter have stalled.

Among the reasons for the lack of improvement in population survival is that only a fraction of people with heart failure receives adequate treatment for the disease. i.e., the full potential of treatment is not yet achieved. Clinical trials are known to recruit a narrow population, usually younger and have few to no background health conditions, which leaves us with an imbalance of data especially among older, sicker patients and women. The patchy evidence makes it challenging for health practitioners to initiate treatment among people who are typically under-represented in clinical trials. In this thesis, the aim was to understand the mismatch between characteristics of clinical trial participants and usual care patients and subsequently how this mismatch affects disease outcomes between the two populations. This objective will be explored and quantified based on eligibility to participate in trials and how these measures impact representativeness and generalizability of trial data. Understanding the degree of mismatch is necessary to find ways to bridge the imbalance in evidence across all patient types. It is important to realise that prevailing challenges to this first step include limited access to clinical trial datasets particularly for pharmaceutical industry-sponsored trials. In this respect, public-private partnerships such as the BigData@Heart collaboration are instrumental in facilitating the work in this thesis, as the working relationship enabled pooling and sharing of patient data between commercial and academic entities

towards the primary goal of enhancing diversity and representation of people with heart failure in clinical trials.

Chapter 1 introduces the topic of clinical trial generalizability and an outline of the projects within this thesis. **Chapter 2** focuses on assessing the eligibility of heart failure registry patients for trials as a measure of trial generalizability and the extent to which the two populations differ. In **chapter 2.1**, we compared the characteristics between five heart failure trials and two patient registries to evaluate the gap between them. We confirmed prior evidence that trial patients were younger by about 10 years, a-third less females, of lower disease severity and had less co-existing medical illness. Although the probability of death appeared lower among trial patients compared to registry patients, this difference was fully explained by disparities in individual characteristics and background disease between the groups. However, when we looked specifically at heart disease-related deaths, they were not the same between the trial and registry groups such that trial patients were 30% more likely to die of heart-related conditions. The fact that known background risk could not fully explain this difference suggests the presence of remaining unmeasured differences between the two patient populations. These differences may arise from other undocumented medical illness or factors relating to whether a person is given the option or chooses to participate in trials.

In **chapter 2.2,** we extended the scope from five trials to all HFrEF trials registered on a clinical trial repository, ClinicalTrials.gov and summarized the main entry criteria to these trials. Rather than taking the earlier approach of side-by-side population comparison, we assessed hypothetical scenarios by applying specific entry criteria of each trial on individuals from an Asian and a European heart failure registry to calculate the percentage which would have entered the trial. We did this for 163 trials and found that only a-fifth of registry patients were eligible to participate in the trials. Overall, both Asian and European registry patients were equally eligible to be enrolled into the trials. Several entry criteria carried more weight in excluding patients from trials. These were previous hospitalization for heart failure, previous heart attack, New York Heart Association class (a measure of heart failure severity) and age. From this study, we demonstrated that it is possible to project the impact of specific trial entry criteria on trial generalizability during design phase of a new study.

On representation by population demography, we identified in **chapter 3.1** that under-representation of females and older persons continue to occur in contemporary HFrEF trials. With available trial data, we found that the direction of trial-registry differences in heart disease-related deaths diverged between males and females; males in trials had 40% higher risk of death from heart-related conditions compared to their real-world counterparts. For females, there were no differences in heart disease-related mortality between trials and registry. This signals that factors beyond defined trial eligibility criteria, such as trial investigator and patient factors, influenced participation rates differentially between males and females.

On a separate perspective of narrowing knowledge gaps in patient outcomes by demography, we presented data on 105 399 hospitalizations for heart failure from Malaysia in **Chapter 3.2**. Absolute number of first hospitalizations for heart failure rose by 52% from 2007 to 2016, driven by the population ageing particularly amongst those aged 60 years and above. This rise in numbers of older persons hospitalized for heart failure highlights a greater need to increase trial data for this subgroup than before. Nevertheless, it is reassuring to note that, when this rise in hospitalizations is subtracted from the expected trends in hospitalizations that is proportional to the growth of the older population, it translates instead to 1 % annual decline in first hospitalizations. This observation suggests that some expected cases have been prevented or delayed by existing measures in heart disease treatment.

Chapter 3.3 further explores the disease progression of these heart failure hospitalizations in the form of repeat hospitalizations and death. We found that, though differences in treatment response in heart failure between race/ethnic groups are known, sparse reporting of race/ethnicity data in trials hampers generalizability evaluation by race/ethnic distributions except for selected countries such as the United States where both trial and observational cohort data were available. In this respect, we showed in the context of the Malaysian population, which is usually categorized as a homogenous racial group of Asians / Southeast Asians in trials, there exists distinct variation in re-hospitalization and death outcomes between ethnicities. Indian heart failure patients had 20% and 13% lower risk of 30-day and 1-year mortality compared to the majority ethnic group, Malays whereas Others, which mainly comprise Indigenous groups have a 30% higher risk of death within 30 days from hospital discharge. This underlines the value of

representing across race/ethnic subgroups when designing trials from a population-wide perspective. Lastly, in (**Chapter 4**), we sum up the present situation on HFrEF trial generalizability and discuss future perspectives toward optimizing generalizability in trials.

NEDERLANDSE SAMENVATTING

Zowel medische als technologische vooruitgang hebben de zorg voor patiënten met hartfalen verbeterd, met name bij de subgroep die bekend staat als hartfalen met verminderde ejectiefractie (HFrEF). Het bewijs waarop de hedendaagse klinische behandelprotocollen zijn gebaseerd is afkomstig uit zorgvuldig opgezette en uitgevoerde klinische trials. Binnen een reeks succesvolle klinische trials uitgevoerd sinds de jaren 90, zijn ten minste vijf geneesmiddelencategorieën effectief gebleken in het verminderen van sterfgevallen naast andere medicijnen die effectief symptomen en ziekenhuisopname verminderen in geselecteerde patiëntengroepen. Op wereldschaal betekent dit dat er een effectieve behandeling beschikbaar is voor meer dan 64 miljoen patiënten met hartfalen. Wanneer de meeste van deze patiënten adequaat wordt behandeld met deze medicatie verwachten we verbetering in overleving van deze groep patiënten. De dalende trend in sterfgevallen bij patiënten met hartfalen werd echter vooral gezien in de periode tussen 1990 en 2000, daarna zijn deze trends tot stilstand gekomen.

Een van de redenen voor het uitblijven van verbetering in de overleving van patiënten met hartfalen is dat slechts een fractie van deze patiënten adequate behandeling krijgt. Dit impliceert dat het volledige potentieel van de hartfalen behandeling nog niet bereikt is. Het is bekend dat klinische onderzoeken een selecte populatie includeren; geïncludeerde patiënten zijn meestal mannelijk, redelijk jong en hebben weinig tot geen verdere comorbiditeiten, waardoor er over oudere, ziekere en vrouwelijke patiënten minder bekend is. Het gebrek aan bewijs maakt het uitdagend om een adequaat behandelplan op te stellen in deze doorgaans ondervertegenwoordigde patiëntengroep binnen klinische trials. Het doel van dit proefschrift is inzicht te verkrijgen in de discrepantie tussen kenmerken van deelnemers aan klinische trials en de algemene hartfalen patiënt-populatie, en om in kaart te brengen hoe deze discrepantie de ziekte-uitkomsten binnen deze twee groepen beïnvloedt. Dit is onderzocht en gekwantificeerd in termen van generaliseerbaarheid (van trial- naar registratie-patiënten), geschiktheid om deel te nemen aan onderzoeken en representatie van verschillende patiëntgroepen binnen deze onderzoeken. Inzicht in de mate van deze mismatch is nodig om het probleem in kaart te brengen en nieuwe methode te ontwikkelen om het gebrek aan medische bewijs voor alle ondervertegenwoordigde groepen te overbruggen. Een belangrijke

uitdaging hierbij is de beperkte toegang tot klinische trial datasets, met name van de door de farmaceutische industrie gesponsorde onderzoeken. Daarom spelen publiek-private samenwerkingen, zoals het BigData@Heart consortium, een belangrijke rol binnen het werk omschreven in dit proefschrift; dit samenwerkingsverband maakte het bundelen en delen van patiëntgegevens tussen commerciële en academische partijen mogelijk met als hoofddoel het vergroten van diversiteit en vertegenwoordiging van mensen met hartfalen in klinische onderzoeken.

In **Hoofdstuk 1** wordt het onderwerp generaliseerbaarheid van klinisch onderzoek geïntroduceerd en een overzicht gegeven van de projecten die staan omschreven in dit proefschrift. **Hoofdstuk 2** gaat over het beoordelen van de geschiktheid van hartfalenregistratiepatiënten voor klinische trials om de mate van generaliseerbaarheid van trials te onderzoeken evenals de mate waarin deze twee populaties verschillen. In **hoofdstuk 2.1** vergeleken we de kenmerken van hartfalen patiënten in vijf gerandomiseerde klinische trials met twee observationele hartfalen registraties. We bevestigden dat in eerdere studies waarbij patiënten geïncludeerd in trials waren ongeveer 10 jaar jonger waren, een derde minder vrouwen bevat, minder ernstig hartfalen hadden en minder co-morbiditeiten hadden. Hoewel de kans op overlijden bij patiënten geïncludeerd in trials lager leek dan bij patiënten geïncludeerd in de hartfalen registraties, werd dit verschil volledig verklaard door verschillen in individuele kenmerken en onderliggend lijden van hartfalen van de groepen. Wanneer we specifiek keken naar sterfgevallen als gevolg van hartaandoeningen, waren deze niet hetzelfde tussen de trial- en registratiegroepen; patiënten geïncludeerd in trials hadden 30% meer kans hadden om te overlijden aan hart-gerelateerde aandoeningen. Het feit dat de bekende risico's dit verschil niet volledig kon verklaren, suggereert de aanwezigheid van nog onbekende verschillen tussen deze twee patiënten groepen. Deze kunnen voortkomen uit andere ongedocumenteerde medische aandoeningen of factoren die verband houden met de vraag of een persoon de optie krijgt of besluit deel te nemen aan klinisch onderzoek.

In **hoofdstuk 2.2** hebben we de reikwijdte uitgebreid van deze vijf onderzoeken naar alle HFrEF-onderzoeken die zijn geregistreerd in het registratie systeem voor klinische trials, ClinicalTrials.gov, en hebben we de belangrijkste inclusiecriteria voor deze trials samengevat. In plaats van de eerdere benadering van

een een-op-een populatievergelijking hebben we hypothetische scenario's getest door specifieke toegangscriteria van elke trial toe te passen op patiënten uit een Aziatische en een Europese hartfalen registratie om daarmee het percentage te berekenen dat voor de trial in aanmerking zou zijn gekomen. We deden dit voor 163 onderzoeken en ontdekten dat slechts één vijfde van de patiënten geïncludeerd in de hartfalen registraties in aanmerking kwam voor deelname aan klinische trials. Over het algemeen kwamen zowel Aziatische als Europese patiënten uit de hartfalen registraties in gelijke mate in aanmerking voor deelname. Verschillende toelatingscriteria wogen zwaarder bij het uitsluiten van patiënten voor deelname aan onderzoek. Hieronder vielen eerdere ziekenhuisopname voor hartfalen, eerder myocardinfarct, klasse van de New York Heart Association (een maatstaaf voor de ernst van hartfalen) en leeftijd. Met deze studie hebben we aangetoond dat het mogelijk is om de impact van specifieke inclusiecriteria voor studies op de generaliseerbaarheid van studies te projecteren tijdens het opzetten van een nieuwe studie.

Wat betreft representatie van bevolking hebben we in **hoofdstuk 3.1** vastgesteld dat ondervertegenwoordiging van vrouwen en ouderen nog steeds voorkomt in hedendaagse HFrEF-onderzoeken. Met de beschikbare onderzoeksgegevens ontdekten we dat bij patiënten geïncludeerd in trials versus registraties de sterfgevallen als gevolg van hartaandoeningen verschilden tussen mannen en vrouwen; mannen geïncludeerd in trials hadden een 40% hoger risico op overlijden door hart-gerelateerde aandoeningen in vergelijking met dezelfde groep geselecteerd in registers, wat een representatie is van de patiënten uit de dagelijkse praktijk. Voor vrouwen waren er geen verschillen in aan hartziekten gerelateerde mortaliteit tussen de trial- en register-populaties. Dit geeft aan dat factoren buiten de gedefinieerde criteria om in aanmerking te komen voor een studie, zoals onderzoek- en patiëntkenmerken, de deelnamepercentages in verschillende mate beïnvloedden tussen mannen en vrouwen.

Gericht op het verkleinen van hiaten in kennis, beschrijven we in **hoofdstuk 3.2** gegevens over 105.399 ziekenhuisopnames voor hartfalen in Maleisië**.** Het absolute aantal eerste ziekenhuisopnames voor hartfalen is tussen 2007 en 2016 met 52% gestegen als gevolg van de vergrijzing van de bevolking, vooral bij 60-plussers. Deze toename van het aantal ouderen dat in het ziekenhuis is opgenomen vanwege hartfalen wijst op een grotere behoefte aan onderzoeksgegevens voor deze

subgroep dan voorheen. Desalniettemin is het geruststellend vast te stellen dat wanneer deze stijging van het aantal ziekenhuisopnames wordt afgetrokken van de verwachte trends in het aantal ziekenhuisopnames, deze evenredig zijn met de trends in vergrijzing, en wordt vertaalt in een jaarlijkse daling van 1% in het aantal eerste ziekenhuisopnames. Deze observatie suggereert dat sommige verwachte gevallen zijn voorkomen of vertraagd door bestaande maatregelen binnen de behandeling van hartziekten.

Hoofdstuk 3.3 gaat verder in op het ziekteverloop bij patiënten met ziekenhuisopnames voor hartfalen in de vorm van herhaalde ziekenhuisopnames en overlijden. We ontdekten dat hoewel verschillen in behandelingsrespons bij hartfalen tussen ras/etnische groepen bekend zijn, schaarste in rapportage van gegevens over ras/etniciteit binnen trials de inschatting m.b.t. generaliseerbaarheid belemmert, behalve in geselecteerde landen zoals de Verenigde Staten waar zowel trial- als observationele cohortgegevens beschikbaar waren voor deze verschillende subgroepen. In dit opzicht toonden we aan dat er binnen de context van de Maleisische bevolking, die gewoonlijk wordt gecategoriseerd als een homogene groep van Aziaten / Zuidoost-Aziaten in trials, duidelijke verschillen bestaan in heropname en overlijden tussen verschillende etnische subgroepen. Indiase patiënten met hartfalen hadden 20% en 13% lager risico op 30-dagen respectievelijk 1-jaars mortaliteit in vergelijking met de etnische meerderheidsgroep, de Maleisiërs. Dit in tegenstelling tot anderen die voornamelijk inheemse populaties omvatten, die een 30% hoger risico op overlijden hebben binnen 30 dagen na het ontslag uit het ziekenhuis. Dit benadrukt de waarde van het vertegenwoordigen van verschillende ras/etnische subgroepen bij het opzetten van onderzoeken vanuit een populatie-breed perspectief. Ten slotte vatten we in **Hoofdstuk 4** de huidige situatie rondom de generaliseerbaarheid van HFrEF-studies samen en bespreken we mogelijkheden voor het optimaliseren van de generaliseerbaarheid binnen onderzoek.

RINGKASAN DALAM BAHASA MELAYU

Kemajuan teknologi dalam perubatan kini telah meningkatkan penjagaan pesakit kegagalan jantung, terutamanya bagi sejenis kegagalan jantung yang dikenali sebagai kegagalan jantung kronik dengan pecahan ejeksi berkurangan (HFrEF). Piawaian penjagaan pesakit adalah berdasarkan bukti kukuh yang diperolehi daripada percubaan klinikal yang direka dan dilaksanakan dengan teliti. Satu siri ujian klinikal yang dikendalikan semenjak tahun 1990-an telah berjaya menghasilkan sekurang-kurangnya lima kategori ubat yang berkesan dalam membantu pengurangan kadar kematian dan menghasilkan ubat yang lain dengan simptom yang kurang serta pengurangan kadar kemasukan hospital di kalangan sebahagian pesakit . Pada skala global, ini menandakan rawatan yang tersedia adalah berkesan untuk lebih kurang 64 juta orang yang mempunyai penyakit kegagalan jantung. Jika kebanyakan pesakit ini dirawat dengan secukupnya dengan ubat-ubatan ini, penurunan progresif dari segi kadar kematian penduduk adalah dijangka. Sesungguhnya, pemerhatian ini jelas dilihat dalam tempoh antara 1990-an dan 2000-an. Akan tetapi, penurunan trend kematian selepas tempoh tersebut telah tergendala.

Antara sebab kekurangan penambahbaikan dari segi penurunan kadar kematian penduduk adalah hanya sebilangan kecil daripada pesakit yang menerima rawatan secara optima. Maka, potensi penuh rawatan masih belum tercapai. Kebanyakkan kajian percubaan klinikal merekrut populasi yang terpilih, iaitu golongan lebih muda dan tidak mempunyai atau hanya satu atau dua komorbid kesihatan. Hal ini menyebabkan kekurangan data berkenaan keberkesanan dan keselamatan ubat-ubatan terutamanya di kalangan pesakit yang berumur, wanita dan golongan yang mempunyai lebih komorbid. Masalah kekurangan data ini menjadi cabaran terhadap pengamal kesihatan untuk memulakan rawatan di kalangan golongan orang yang biasanya kurang diwakili dalam ujian klinikal. Dalam tesis ini, matlamatnya adalah untuk memahami perbezaan serta jurang di antara peserta percubaan klinikal dan pesakit biasa bagi kegagalan jantung dan seterusnya bagaimana jurang ini mempengaruhi prognosis penyakit antara kedua-dua populasi tersebut. Objektif ini akan diterokai dan dikaji berdasarkan kelayakan penglibatan dalam ujian klinikal dan bagaimana langkah ini dapat mempengaruhi aplikasi data ujian klinikal secara umum. Pemahaman tahap ketidakpadanan ini adalah penting

bagi usaha penyelidikan untuk saling melengkapi jurang bukti kajian bagi semua variasi pesakit yang mengalami kegagalan jantung. Adalah penting untuk menyedari bahawa cabaran lazim untuk langkah pertama ini termasuk kekangan akses kepada set data percubaan klinikal terutamanya bagi kajian percubaan klinikal yang dari tajaan industri farmaseutikal. Dalam konteks ini, kolaborasi di antara pihak awam dan swasta seperti kerjasama BigData@Heart memainkan peranan penting dalam memudahkan perkongsian data pesakit antara entiti komersial dan akademik ke arah matlamat utama iaitu bagi meningkatkan kepelbagaian dan perwakilan orang yang mengalami kegagalan jantung dalam percubaan klinikal ubat-ubatan.

Bab 1 memperkenalkan topik mengaplikasikan data percubaan klinikal secara umum dan rangka bagi projek dalam tesis ini. Bab 2 pula memberi tumpuan kepada menilai kelayakan penglibatan pesakit kegagalan jantung biasa dalam percubaan klinikal sebagai ukuran aplikasi percubaan klinikal secara umum dan sejauh mana perbezaannya antara kedua-dua populasi tersebut. Dalam **Bab 2.1**, kami membandingkan ciri-ciri pesakit antara lima ujian klinikal kegagalan jantung dan dua registri pesakit biasa kegagalan jantung bagi menilai jurang antara mereka. Kami mengesahkan bukti terdahulu bahawa pesakit yang terlibat dalam percubaan klinikal adalah lebih muda dalam lingkungan 10 tahun berbanding dengan pesakit biasa dan perwakilan golongan wanita adalah rendah, di mana bilangannya adalah 30 peratus lebih rendah daripada perwakilan di kalangan pesakit biasa. Di samping itu, tahap keparahan penyakit yang lebih rendah di kalangan peserta percubaan klinikal apabila dibandingkan dengan pesakit kegagalan jantung yang biasa diketemui di fasiliti kesihatan. Walaupun kebarangkalian kematian kelihatan lebih rendah di kalangan pesakit percubaan klinikal berbanding pesakit biasa daripada registri, perbezaan ini dapat dijelaskan sepenuhnya dari segi ciri individu dan penyakit latar belakang antara dua kumpulan ini. Walaubagaimanapun, apabila kami menjurus kepada kematian yang berkaitan dengan penyakit jantung, peratus di antara dua populasi tersebut adalah berbeza, iaitu peserta percubaan klinikal mempunyai kebarangkalian 30% lebih tinggi meninggal dunia akibat penyakit kardiovaskular. Perbezaan ini mungkin berpunca daripada penyakit lain yang tidak didokumenkan atau faktor lain yang berkaitan kecenderungan untuk mengambil bahagian dalam percubaan klinikal. Dalam **bab 2.2**, kami memperluaskan skop pencarian daripada lima percubaan klinikal kepada semua percubaan klinikal HFrEF yang didaftarkan pada repositori percubaan klinikal, ClinicalTrials.gov dan

meringkaskan kriteria kemasukan utama kepada percubaan ini. Berbanding pendekatan dalam bab 2.1, dalam bab ini kami menilai senario andaian dengan menggunakan kriteria kemasukan khusus setiap percubaan klinikal ke atas individu dari data registry kegagalan jantung daripada Asia dan Eropah untuk mengira peratusan yang layak memasuki percubaan klinikal. Langkah ini dilakukan ini untuk 163 ujian dan didapati bahawa hanya satu perlima daripada pesakit registri yang layak untuk mengambil bahagian dalam percubaan klinikal. Secara keseluruhan, tiada perbezaan dari segi kelayakan menyertai percubaan klinikal di antara pesakit registri daripada Asia dan Eropah. Terdapat beberapa kriteria kemasukan yang lebih cenderung untuk mengecualikan pesakit biasa daripada percubaan klinikal. Kriteria ini termasuk sejarah kemasukan hospital kerana kegagalan jantung, sejarah kemasukan hospital kerana serangan jantung, kategori Persatuan Jantung New York (ukuran tahap keparahan kegagalan jantung) yang lebih serius, dan faktor umur.

Mengenai perwakilan mengikut demografi penduduk, kami telah mengenal pasti dalam **bab 3.1** bahawa perwakilan wanita dan warga emas yang tidak mencukupi sering berlaku dalam percubaan klinikal kegagalan jantung. Dengan data percubaan klinikal yang sedia ada, kami mendapati bahawa perbezaan kadar kematian di antara peserta percubaan klinikal kegagalan jantung dan pesakit biasa kegagalan jantung terbahagi antara golongan lelaki dan perempuan yakni golongan lelaki dalam percubaan klinikal mempunyai risiko kematian 40% lebih tinggi dari pesakit golongan lelaki pesakit biasa. Bagi wanita, tiada perbezaan kadar kematian berkaitan penyakit jantung antara pesakit percubaan klinikal dan pesakit registri. Hal ini menunjukkan bahawa faktor di luar kriteria kelayakan, seperti faktor penyelidik percubaan klinikal dan faktor pesakit telah mempengaruhi kadar penyertaan secara berbeza di antara golongan lelaki dan perempuan.

Daripada perspektif yang berbeza, kami membentangkan data mengenai 105 399 kemasukan ke hospital untuk kegagalan jantung dari Malaysia dalam bab **3.2**. Bilangan mutlak kemasukan pertama ke hospital untuk kegagalan jantung meningkat sebanyak 52% dari tahun 2007 hingga 2016, dimana ianya didorong oleh faktor peningkatan umur populasi terutamanya di kalangan mereka yang berumur 60 tahun ke atas. Peningkatan bilangan warga emas yang masuk ke hospital kerana kegagalan jantung ini menyerlahkan keperluan untuk meningkatkan data percubaan klinikal bagi golongan ini berbanding tahun-tahun sebelum ini. Apabila faktor umur pesakit dikecualikan dalam analisis data, didapati bahawa kadar kemasukan hospital

kerana kegagalan jantung mengalami penurunan sebanyak 1% setiap tahun. Pemerhatian ini menunjukkan bahawa sebahagian kes kemasukan hospital dapat dijangka, dicegah atau ditangguhkan oleh langkah-langkah sedia ada dalam rawatan penyakit jantung.

Bab 3.3 meneroka lebih lanjut perkembangan penyakit kegagalan jantung ini dari segi kemasukan ke hospital secara berulangan dan kematian. Walaupun terdapat perbezaan ketara dari segi hasil rawatan kegagalan jantung di antara kumpulan kaum/etnik, kekurangan dokumentasi berkenaan kaum/etnik di kalangan peserta percubaan klinikal menghalang penilaian aplikasi secara umum mengikut kaum/etnik kecuali untuk negara yang terpilih seperti Amerika Syarikat di mana data kedua-dua percubaan klinikal dan data kohort pemerhatian tersedia ada. Dalam konteks penduduk Malaysia, kami menunjukkan yang biasanya ianya dikategorikan sebagai satu kumpulan kaum homogen Asia / Asia Tenggara dalam percubaan klinikal, masih terdapat perbezaan kadar kemasukan semula hospital dan hasil kematian di antara etnik. Pesakit kegagalan jantung berkaum India mempunyai risiko 20% dan 13% lebih rendah untuk kematian dalam 30 hari dan 1 tahun setelah discaj dari hospital berbanding kumpulan etnik majoriti, iaitu kaum Melayu manakala kaum Lain-lain, yang kebanyakannya terdiri daripada kumpulan Orang Asli mempunyai risiko kematian 30% lebih tinggi dalam tempoh 30 hari dari discaj hospital. Hal ini menggariskan kepentingan mewakili semua kumpulan kecil kaum/etnik dalam populasi percubaan klinikal daripada perspektif seluruh penduduk. Sebagai pengakhiran, dalam (**Bab 4**), kami merumuskan situasi semasa secara umum tentang aplikasi percubaan klinikal serangan jantung dan membincangkan perspektif masa depan ke arah mengoptimumkan perwakilan peserta percubaan klinikal bagi meningkatkan aplikasi data percubaan klinikal secara umum

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ABOUT THE AUTHOR

Yvonne Mei Fong Lim was born on October 2, 1985 in Petaling Jaya, Malaysia. She obtained her pharmacy degree from the University of Strathclyde, United Kingdom in 2008. Subsequently, she worked as a pharmacist with the Ministry of Health Malaysia at the Sultan Haji Ahmad Shah hospital between 2008 and 2012. Then, she joined the Institute for Clinical Research (ICR), a research organization within the same ministry. Here, she was involved in national surveys and implementation research focussing on primary health care. From 2014 to 2016, she pursued a Master of Information Systems at the National University of Malaysia under a scholarship from the Ministry of Health. Then, she participated as a fellow in the 50th International Ten-day Teaching Seminar on Cardiovascular Epidemiology and Prevention in Goa, India in 2018 and this has sparked an interest in cardiovascular research. In March 2019, Yvonne started as a PhD candidate at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU) under the supervision of prof. dr. Folkert W Asselbergs, prof. dr. Diederick E Grobbee, dr. Ilonca Vaartjes and dr. Stefan Koudstaal. The research project is funded by BigData@Heart and the UMCU Global Health Support Program; it represents work to understand and improve generalizability of heart failure trials based on data from Europe, Malaysia as well as other parts of Asia. During the PhD program, she completed a postgraduate Master of Clinical Epidemiology in 2022. Currently, she works as a researcher at ICR, National Institutes of Health, Malaysia focusing on atherosclerotic cardiovascular disease.

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