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ORIGINAL RESEARCH

Usefulness of Heart Failure Categories Based on Left Ventricular Ejection Fraction

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BACKGROUND: Heart failure guidelines have recently introduced a narrow category with mildly reduced left ventricular ejection fraction (LVEF) (heart failure with mildly reduced ejection fraction; LVEF 41%–49%) between the previous categories of reduced (heart failure with reduced ejection fraction; LVEF ≤40%) and preserved (heart failure with preserved ejection fraction; LVEF ≥50%) ejection fraction. Grouping of continuous measurements into narrow categories can be questioned if their variability is high.

METHODS AND RESULTS: We constructed a cohort of all 9716 new cases of chronic heart failure with an available LVEF in Stockholm, Sweden, from January 1, 2015, until December 31, 2020. All values of LVEF were collected over time, and patients were followed up until death, moving out of Stockholm, or end of study. Mixed models were used to quantify within-person variance in LVEF, and multistate Markov models, with death as an absorbing state, to quantify the stability of LVEF categories. LVEF values followed a normal distribution. The SD of the within-person variance in LVEF over time was 7.4%. The mean time spent in any LVEF category before transition to another category was on average <1 year for heart failure with mildly reduced ejection fraction. Probabilities of transitioning between categories during the first year were substantial; patients with heart failure with mildly reduced ejection fraction had a probability of <25% of remaining in that category 1 year later.

CONCLUSIONS: LVEF follows a normal distribution and has considerable variability over time, which may impose a risk for underuse of efficient treatment. The heart failure with mildly reduced ejection fraction category is especially inconstant. Assumptions of a patient's current LVEF should take this variability and the normal distribution of LVEF into account.

Key Words: heart failure ■ left ventricular ejection fraction ■ treatment decisions ■ variability

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Heart failure is associated with high mortality and morbidity, as well as being 1 of the costliest diseases to society.[1,2] Current heart failure guidelines[3,4] mandate treatment based on patients' left ventricular ejection fraction (LVEF), categorized as heart failure with reduced ejection fraction (HFrEF; LVEF ≤40%), heart failure with preserved ejection fraction (HFpEF; LVEF ≥50%), and the relatively recent addition, heart failure with mildly reduced ejection fraction (HFmrEF; LVEF 41%–49%).[3,4] These LVEF-based groups could be reasonable if the LVEF distribution were bimodal,[5–7] reflecting 2 clearly different groups determined by the cause of the heart failure.[8–10] They are further motivated by the development of much of the evidence behind current heart failure treatments in groups defined by low LVEF. Recent studies of SGLT2 (sodium-glucose transport protein 2) inhibitors have demonstrated effects of those drugs on

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CLINICAL PERSPECTIVE

What Is New?

- Left ventricular ejection fraction has a normal distribution and a considerable variability over time in the population with heart failure.
- The variability persists also when excluding patients with substantial changes in underlying disease.
- The heart failure with mildly reduced ejection fraction category is especially inconstant, with less than a year on average spent in the category before transitioning to another category or death, regardless of age and sex.

What Are the Clinical Implications?

- Clinicians should take this variability of left ventricular ejection fraction and its normal distribution into account when using left ventricular ejection fraction for treatment decisions, to minimize the risk of underuse of treatment.

Nonstandard Abbreviations and Acronyms

HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction

important efficacy outcomes across the LVEF spectrum,[11,12] calling these LVEF categories into question and reigniting the discussion of the shape of the LVEF distribution.[9,11,13]

Because heart failure is a clinical syndrome with many causes, heterogeneity between patients is expected. Furthermore, biological variability within patients in measures such as LVEF is substantial,[14–16] with additional variability attributable to the echocardiography method,[17–20] inconsistencies in imaging quality, and experience of the examiner.[21,22] Categorization of continuous variables with substantial variability into narrow groups, and basing treatment decisions on such categories, is problematic.[18]

We aimed to determine the shape of the LVEF distribution and quantify the stability of LVEF categories over time in a large real-world population with heart failure, to assess the usefulness of LVEF categories for treatment decisions.

METHODS

We used a population-based observational cohort study of all new cases of chronic heart failure in Stockholm in the CELOSIA database. The CELOSIA database comprises Swedish patients with heart failure, chronic kidney disease, or diabetes recorded at any time between January 1, 2000, and December 31, 2020. Data in the CELOSIA database are obtained from the national patient registry, cause of death registry, Swedish prescribed drug registry, The Stockholm Healthcare Data Warehouse, and electronic health records (EHRs) from Stockholm (private health care providers excluded). Individual patient-level data from the national registers and regional data sources were linked using the personal identification number.[23]

Ethical Approval

This study was approved by the regional Swedish Ethics Review Authority (approval 2020-03850), and informed consent was waived for this study. Because of the sensitive nature of the data collected for this study, data cannot be shared. Code can be made available by the corresponding author upon reasonable request.

Study Sample

All new cases of heart failure between January 1, 2015, and December 31, 2020, having an available LVEF measurement recorded 90 days before or after the date of diagnosis were identified in the CELOSIA database. A diagnosis of heart failure, as main cause or contributing cause of health care contact, was determined as an *International Classification of Diseases, Tenth Revision* (*ICD-10*)[24] code of: I50 (heart failure), I11.0 (hypertensive heart disease with heart failure), I13.0 (hypertensive heart and renal disease with heart failure), or I13.2 (hypertensive heart and renal disease with heart and renal failure). Patients were required to have at least 1 day of follow-up, starting at the index date of first heart failure diagnosis, to be eligible. Exclusion criteria were age <18 years or lack of a valid Swedish personal identification number. For included patients, all available LVEF records were obtained regardless of value. Patients were followed up from their first heart failure diagnosis until the first instance of death, moving out of Stockholm, or end of study (December 31, 2020).

As a sensitivity analysis, a subgroup was defined with patients free from changes in underlying disease status, procedures, or both during the 5-year follow-up after diagnosis, keeping those variables constant that were expected to lead to large within-patient variability in LVEF. The underlying variables included acute myocardial infarction, any new valve disorder, incident

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atrial fibrillation, heart transplant or valve surgery, pericarditis/myocarditis, and incident chemotherapy or radiotherapy. The time period was extended for acute myocardial infarction to also cover 6 months before heart failure diagnosis, but not for any of the other variables. In addition, 2 sensitivity analyses were performed: 1 with the exclusion of heart transplant and left ventricular assist device, and 1 with strictly numerical LVEF.

Variable Definitions

All diagnoses and procedures were based on *ICD-10*[24] or clinical procedure codes.[25] Codes available from primary care, specialized outpatient care, and inpatient care were used to define comorbidities unless otherwise stated, including both primary and nonprimary diagnoses. Dispensations of selected treatments were defined on the basis of the Anatomical Therapeutic Chemical Classification System codes.[26] Socioeconomic status was extracted from the Mosaic system, which is categorized into 3 levels: high, medium, or low. Baseline characteristics were extracted from the CELOSIA database at inclusion and are presented in the Table.

LVEF Measurements

EHRs from Stockholm with LVEF measurements were extracted in both structured numerical format and unstructured free-text format. EHR was searched for the terms "echocardiography" and "EF (ejection fraction)," and the corresponding value was extracted. The free-text format allowed the unstructured values to be an exact number, a range of values, or a category. Measurements in unstructured format were manually curated; numerical measurements were favored over categorical definitions, and calculated measurements were favored over eyeballing. Exact numeric or semiquantitative LVEF values were extracted where available. If the patients had multiple measurements within 14 days, the latest value was assumed to be the measurement for treatment decisions and was therefore used in this study. The following categories were defined according to current European Society of Cardiology[3] and American College of Cardiology/American Heart Association guidelines[4]: HFpEF ≥50%, HFmrEF 41% to 49%, and HFrEF ≤40%. Where semiquantified EF or intervals were observed, they were categorized according to the guidelines. When an interval was not completely coherent to a guideline category (eg, 40%–49%), the patient was classified with the category with most overlapping, in this case HFmrEF. The free-text observations were reviewed and categorized on the basis of predefined categories; preserved EF was categorized as HFpEF, mildly reduced EF as HFmrEF, and moderate and severely reduced EF

Table. Baseline Characteristics

Characteristic	Value (n=9716)
Age, median (IQR), y	73.9 (64.1–81.5)
Women, n (%)	3898 (40.1)
Socioeconomic status, n (%)	
Low	3718 (38.3)
Middle	4058 (41.8)
High	1931 (19.9)
Smoker, n (%)	
Current	728 (7.5)
Previous	2353 (24.2)
Never	2811 (28.9)
Missing	3022 (31.1)
LVEF classification, n (%)	
≤40%	4050 (41.7)
41%–49%	2149 (22.1)
≥50%	3517 (36.2)
Comorbidities, n (%)	
Ischemic heart disease	4017 (41.3)
Acute coronary syndrome	2556 (26.3)
CABG	418 (4.3)
PCI	1954 (20.1)
Stroke	1550 (16.0)
Atrial fibrillation	4491 (46.2)
Valve disease	1800 (18.5)
Peripheral artery disease	1222 (12.6)
Diabetes (types 1 and 2)	2524 (26.0)
CKD	1688 (17.4)
Cancer	2793 (28.7)
Clinical and laboratory data	
Systolic blood pressure, median (IQR), mm Hg	135.0 (120.0–151.0)
Diastolic blood pressure, median (IQR), mm Hg	80.0 (70.0–90.0)
Heart rate, median (IQR), beats/min	81.0 (70.0–99.0)
BMI, median (IQR), kg/m^2	26.5 (23.4–30.2)
NT-proBNP, median (IQR), mmol/L	2416 (1020–5671)
eGFR, median (IQR), mL/min/1.73 m^2	61.8 (47.5–74.4)
Hemoglobin, median (IQR), mmol/L	132 (118–145)
Drug therapy, n (%)	
Guideline-directed medical treatment*	
ACEi	4976 (51.2)
ARB	3120 (32.1)
ARNI	273 (2.8)
β-Blockers	8034 (82.7)
MRA	2995 (30.8)
SGLT2i	236 (2.4)

(*Continued*)

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Table. Continued

Characteristic	Value (n=9716)
Loop diuretics	5929 (61.0)
Digoxin	1071 (11.0)
Nitrates	2191 (22.6)
Anticoagulants	3772 (38.8)
Antiplatelets	3845 (39.6)
Medical facility of first heart failure diagnosis, n (%)	
Primary care	712 (7.3)
Outpatient specialized care	2529 (26.0)
Inpatient specialized care	6475 (66.6)

Socioeconomic status is the last value before index within 10 years. Comorbidities are any previous diagnosis before index. All clinical and laboratory results are the last value within a year before index date. Drug therapy is medical dispensary take out 6 months after index. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; and SGLT2i, sodium-glucose transport protein 2 inhibitor.

*According to European Society of Cardiology and American College of Cardiology/American Heart Association guidelines.

as HFrEF. A small number of records could not be assigned to a single category and were omitted.

The time frame of LVEF measurement was set to 90 days before or after heart failure diagnosis as an adaptation to the clinical setting, where not all patients have the opportunity to do the echocardiography in close relation to a physician's appointment.

Measurement intervals were defined as the time between 2 LVEF measurements, at least 15 days apart. An interval event was defined as new occurrence of acute myocardial infarction, any new valve disorder, incident atrial fibrillation, heart transplant or valve surgery, pericarditis/myocarditis, and incident chemotherapy or radiotherapy during the measurement interval. Acute myocardial infarction was the only diagnosis set during hospitalization, and the other could be set in primary care, hospital visits, or hospitalization.

Statistical Analysis

R, 3.6.0 or 4.1.1,[27] was used for all analysis. Continuous variables were described using means and SDs or medians and interquartile ranges, depending on distribution. Categorical variables were described as numbers and percentages.

LVEF Distributions

The distribution function of LVEF was estimated in a maximum likelihood framework, which has been described previously,[28] where each LVEF recording (numeric or semiquantitative/categorical) was set to lie within an interval as follows: intervals for numeric values rounded to nearest 5% were set to value ±2.5%, intervals for numeric values not rounded to nearest 5% were set to value ±0.5%, and intervals for semiquantitative values were set to their stated upper/lower limit (eg, ≥50 to 50–99). LVEF was set to be bounded by 1 and 99. The distribution of numeric and mixed numeric and categorical recordings was estimated. The distribution of numeric recordings was also investigated using Shapiro-Wilk normality test and a Q-Q plot.

LVEF Within-Person Variability

A linear mixed model allowing a mixture of numeric or semiquantitative/categorical LVEF values as the dependent variable was fit,[29] including a fixed effect intercept, a fixed effect slope for time since heart failure diagnosis, and a random intercept at the patient level. A model with/without a restricted natural cubic spline for the fixed effect for time was tested. The trend in the LVEF the first year after heart failure diagnosis was modeled for all patients with at least 1 year of follow-up who had a follow-up measurement of LVEF at any time after the heart failure diagnosis.

LVEF Category Transitions

The data are interval censored (ie, the exact time of a transition between LVEF states is unknown and can have occurred at any time within an unobserved interval between the LVEF assessments). A multistate Markov model for interval-censored data[30] was fit to model transitions over time between transient states (HFpEF, HFmrEF, and HFrEF) and the absorbing state death. The R package msm, version 1.7, was used for the multistate models (functions msm, prevalence.msm, totlos.msm, pmatrix.msm, and sojourn.msm). The heart failure categories were used as separate states because of the differences in clinical treatment recommended by current guidelines.[3,4] The model was adjusted for age at time of heart failure diagnosis and sex. Piecewise constant transition intensities were assumed between time cutoffs at 3 and 18 months over the 5-year follow-up period. Allowed transitions in continuous time were modeled to be HFpEF->{HFmrEF, death}, HFmrEF->{HFpEF, HFrEF, death}, and HFrEF->{HFmrEF, death}. All CIs were estimated through a normal approximation. For the specific method used for interval-censored data, we refer to a previous publication.[30] The mean sojourn time was first calculated from a separate model assuming constant transition intensities over the entire follow-up period. A final model of the sojourn time was then fit with a time cutoff at 18 months, selected so that each time segment was longer than the expected sojourn time from the model without time splitting. The mean sojourn time was then

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calculated within each time segment (0 to <18 months and ≥18 months to 5 years after first heart failure diagnosis). All models were adjusted for age and sex.

RESULTS

We included 9716 patients with a new diagnosis of heart failure and available LVEF (Figure S1). The median age at time of diagnosis was 73.9 years, and 40.1% were women. The baseline characteristics are presented in the Table. Median follow-up time was 2 years, and 6933 patients (71%) had a follow-up of at least 1 year. Of LVEF, 52% was structured numeric and 48% was unstructured free-text format. A total of 26 391 patients were excluded because of lack of record of LVEF 90 days before or after diagnosis (Table S1). These patients had a median age of 80.2 years, 50.7% were women, and 29% had their first diagnosis of heart failure set in a primary care facility.

A total of 4680 patients had at least 2 measurements of LVEF during the study period, which resulted in

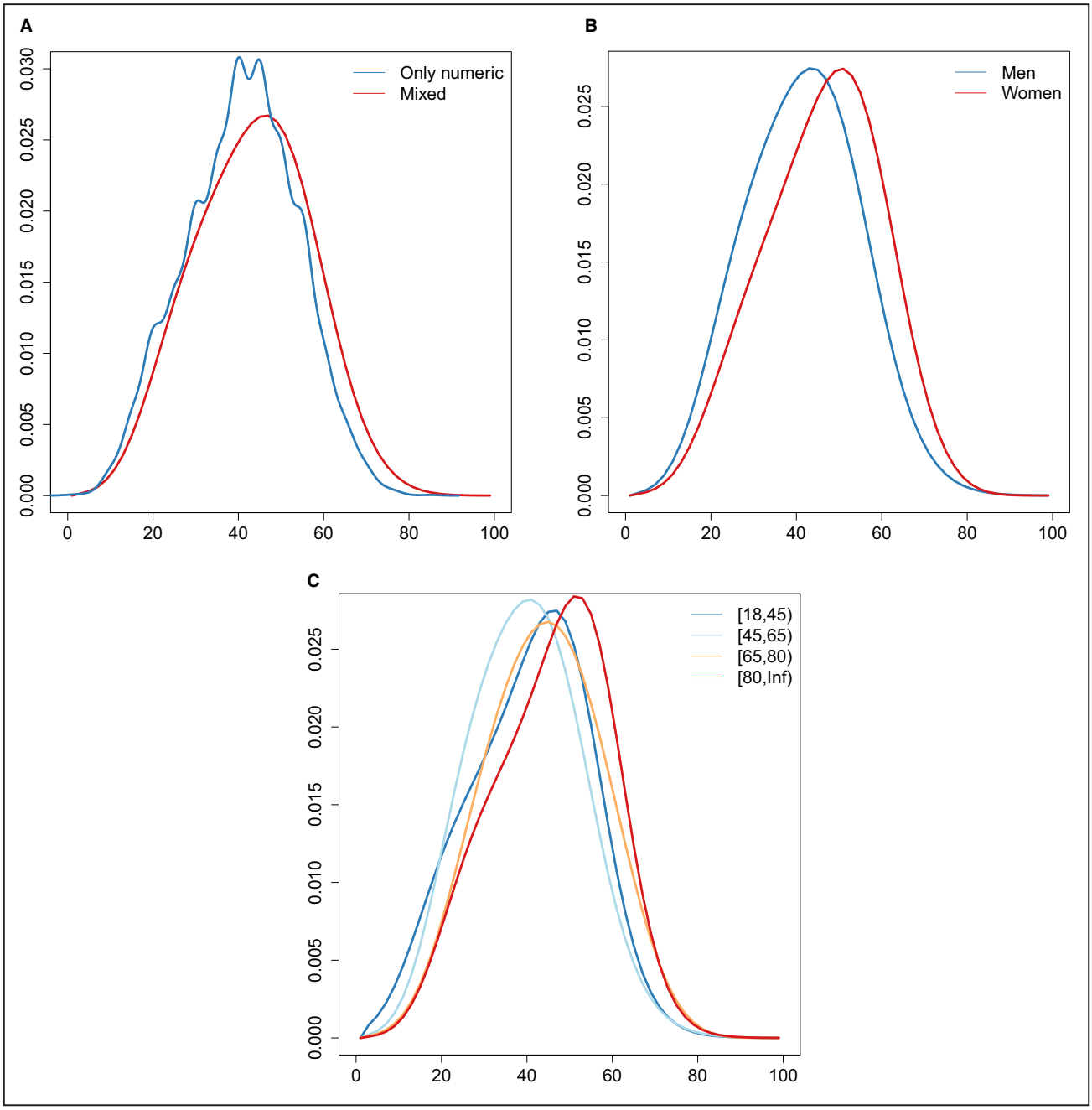

Figure 1. Distribution of LVEF at heart failure diagnosis.
A, Density plot of LVEF distribution based on numeric values only and the most likely distribution from a mixture of numeric and categorical LVEF measurements. The most likely distribution from a mixture of numeric and categorical LVEF measurements stratified by sex (**B**) and by age group in years (**C**) is shown. LVEF indicates left ventricular ejection fraction.

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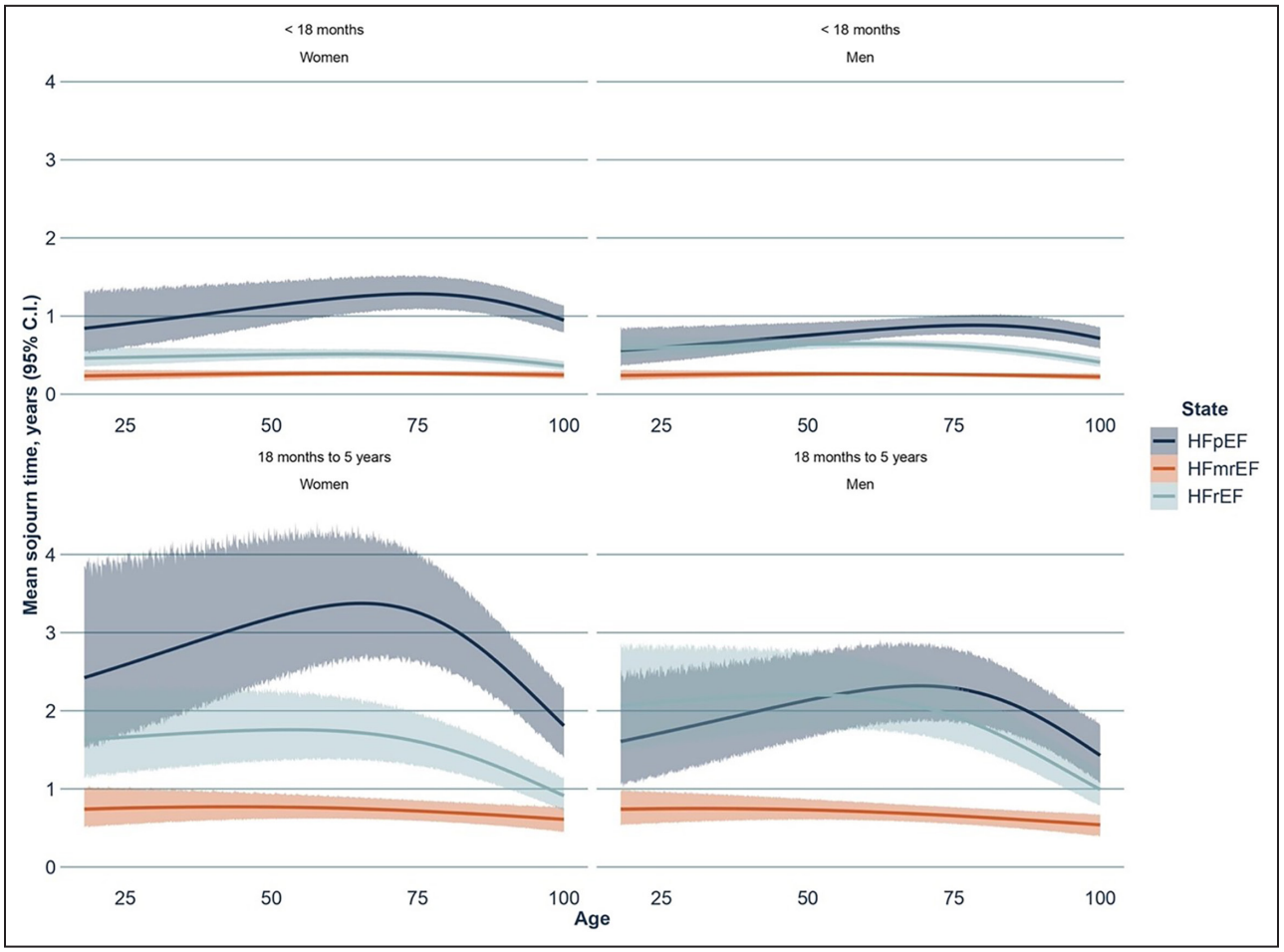

Figure 2. Estimated average time spent in LVEF state (HFpEF, HFmrEF, or HFrEF) before transitioning to new state or death, by age, sex, and time period.
Mean sojourn time is average time spent in LVEF state before transitioning to new state or death (absorbent state). HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

31 094 measurement intervals with a median of 3 measurement intervals (Figure S2). During 11 182 measurement intervals (36.0%), an interval event occurred; and during 19 912 intervals (64.0%), no event occurred. The distribution of the interval event resulting in an increase, no change, or reduction in LVEF is shown in Table S2.

LVEF was normally distributed, in the whole study sample as well as in categories based on age or sex (Figure 1), with a Shapiro-Wilk W=0.99 (Q-Q plot in Figure S3). The distribution of a combination of numeric and categorized LVEF was similar to a distribution of only numeric LVEF. The residual SD of the within-person variance in LVEF was 7.4%. More detailed results from the mixed model are provided in Table S3.

The time spent in the HFmrEF state before transitioning to another state (including death) was on average <1 year in both women and men, regardless of age for both the first 18 months after diagnosis as well as for the time period from 18 months to end of follow-up. Patients with HFpEF had the longest sojourn time, and patients with HFrEF had estimates in between those with HFpEF and HFmrEF (Figure 2).

The total time spent in each LVEF category, as a function of initial category, sex, and age, is presented in Figure 3. Women spent more time in HFpEF than men in all age groups, regardless of initial state.

Figure 4 demonstrates the 1-year probabilities of transitioning from the initial state to any state. Patients with HFrEF had a probability of 40% for men and 30% for women to be in the HFrEF category after 1 year. For patients with HFmrEF, the probability of being in the HFmrEF category 1 year later was <25%, for both men and women. Men with HFpEF had a probability of ≈55% of being in the HFpEF category after 1 year, and women had a probability of ≈65%. Men with initial classification as preserved or mildly reduced EF had a probability of ≈40% to transcend to HFrEF after 1 year. The probability for the same transition in women was ≈25%.

The subgroup without substantial changes in underlying disease comprised 4567 patients, 47% of the

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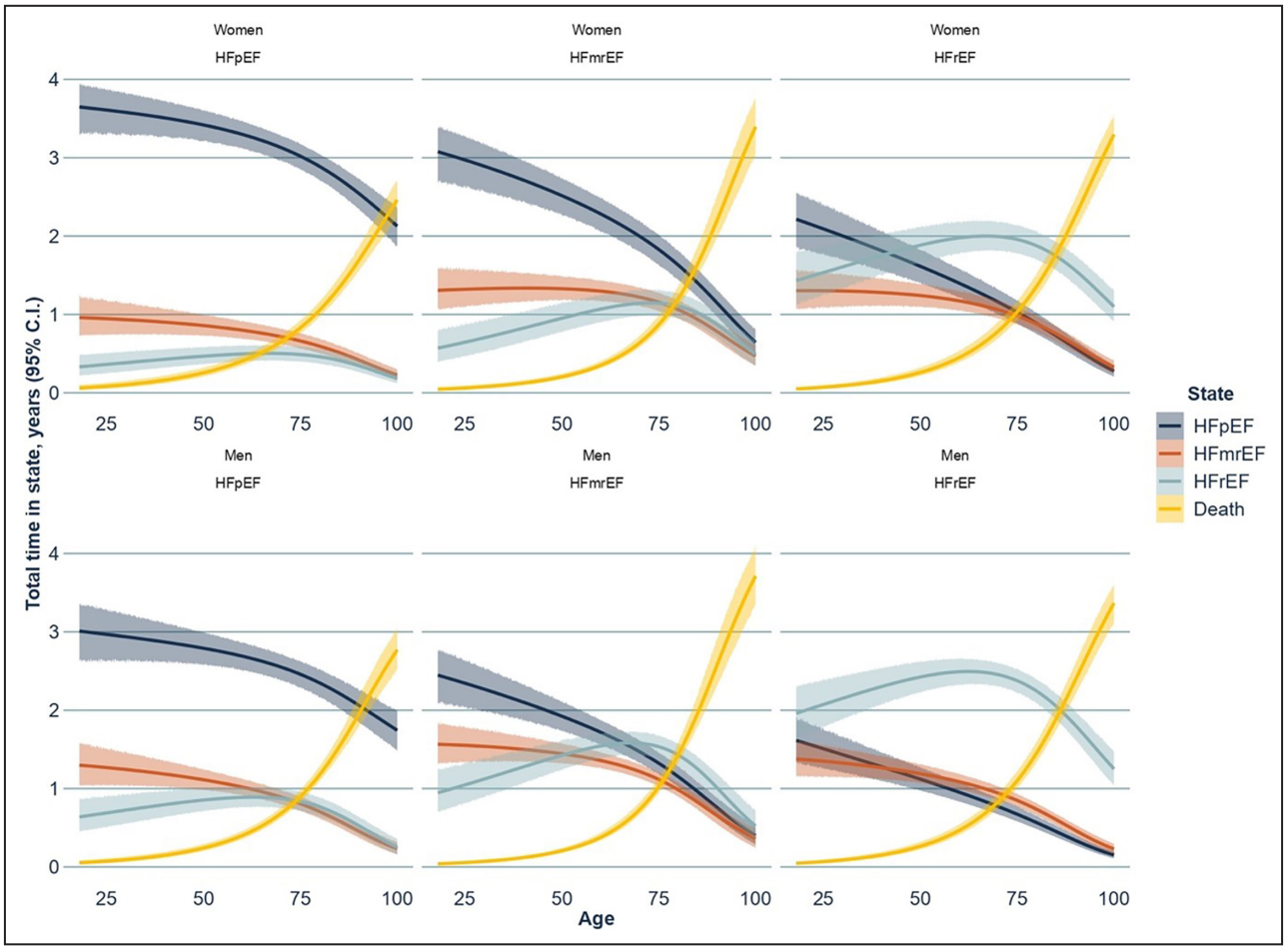

Figure 3. Estimated total time spent in a state over 5 years with panels by entry state, age, and sex.
HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

total study population. In this subgroup, LVEF followed a normal distribution (Figure S4), and the average time spent in each state before transition to new state or death was similar to the whole study population, with a time cutoff at 24 months (Figure S5). Similar results to the main group were seen in the sensitivity analysis when excluding patients with heart transplantation or left ventricular assist device in average time spent in each state (Figure S6) and 1-year probability of transitioning from initial state to any state (Figure S7).

Results in the group with only numerical LVEF measurements were similar to the whole sample in regards to the average time spent in each state before transition to new state or death (Figure S8) and 1-year probability of transitioning from initial state to any state (Figure S9).

DISCUSSION

This large cohort study of all patients with incident heart failure in a large regionally defined population shows that LVEF follows an unquestionably normal distribution in heart failure. The within-person variability in LVEF over time in these patients is considerable, resulting in a short time period spent in any LVEF-based category before transitioning out of it; the narrower the LVEF category, the shorter the time spent in it. This calls into question the usefulness of affixing treatment guidelines to such transient LVEF categories.

The distribution of LVEF in the population with heart failure is debated. The notion of 2 distinct groups stems primarily from samples with acute decompensation or hospitalization for heart failure,[6,8] limited by small sample sizes or a tertiary care nature of the cases. LVEF has been shown to vary up until a year after acute decompensation.[14] This selection therefore creates a subgroup conditioned on decompensation within the population with heart failure, which can create a collider bias.[31,32] Collider bias also plagues baseline distributions in clinical trials with combinations of inclusion criteria, as demonstrated in the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction study, where patients with LVEF 31% to 40% were harder to include because

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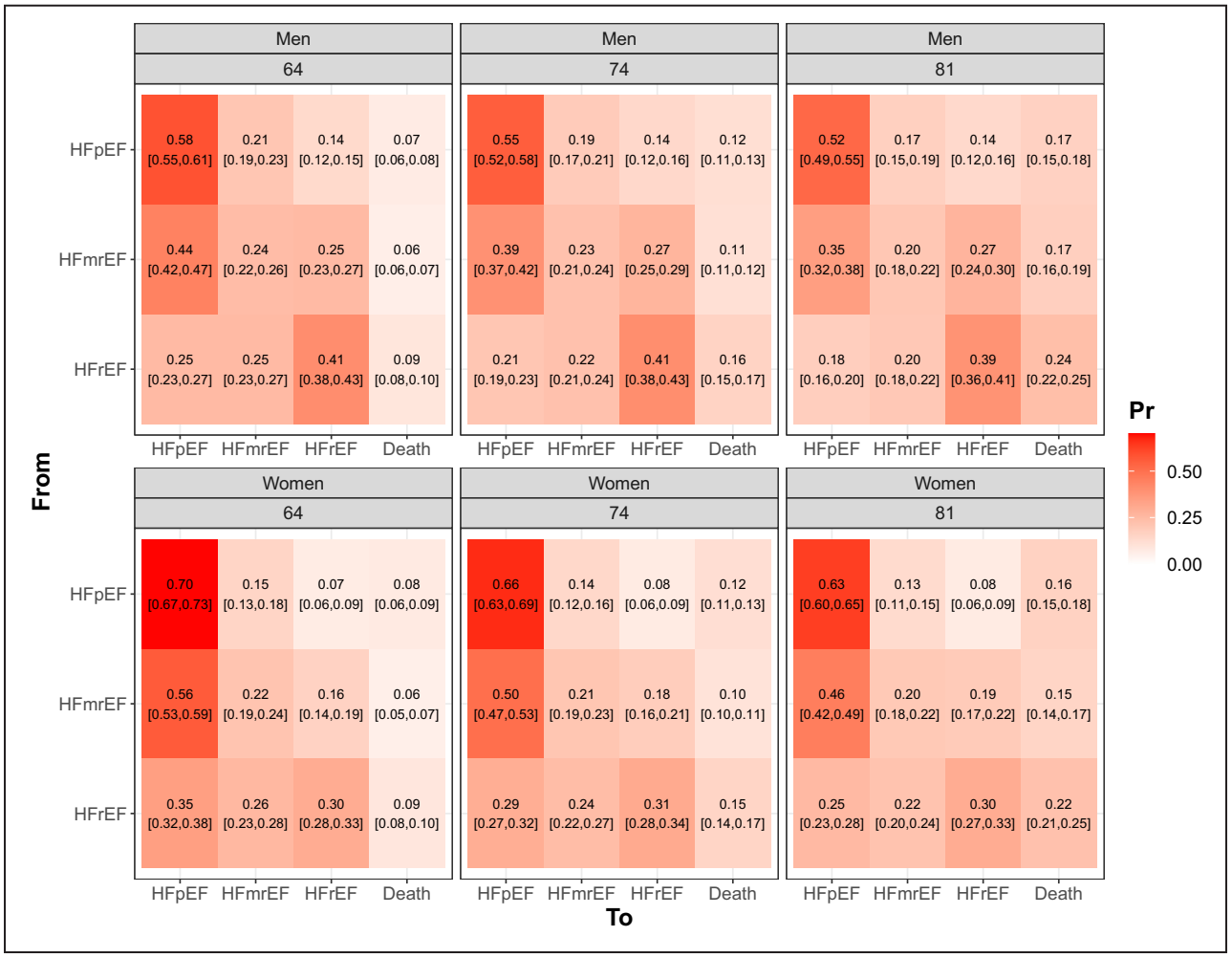

Figure 4. One-year transition probability from state (*y* axis) to state (*x* axis), with panels by age and sex.
HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and Pr, probability.

of the requirement of high NT-proBNP (N-terminal pro-B-type natriuretic peptide) for inclusion of patients in this LVEF range in EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction, creating a bimodal distribution.[12] The setting used in the present study, with broad coverage of primary and specialized care, both in hospitals and outpatient clinics, allows for an unconditioned sample of the entire diagnosed population with heart failure. A unimodal distribution of LVEF has also been shown in some previous large prospective cohorts in other settings,[13,33] seemingly with similarly low risk of collider bias.

Our findings of considerable within-person variability in LVEF are in line with previous findings of dynamic trajectories in HFrEF, HFmrEF,[15,16] and HFpEF groups.[5,34] The variability and the time period spent in each state was not affected when patients with substantial changes in underlying disease were excluded or when restricted to solely numerical values, as sensitivity analysis. Variability of LVEF is, partly, dependent on the reproducibility of LVEF assessments, which has been shown to depend on the performance of the examiner,[21,22] the image quality and interpretation by the examiner,[18,19] and even the method used for automated calculation.[35] The tendency to round to the nearest 5% when performing a visual assessment with echocardiography also highlights the dilemma with using a narrow category of <10%.[36] Another aspect affecting reproducibility is the difficulty of being unbiased as an examiner if serial unblinded measurements hin the same patient, or if you also are the treating physician.

The not insignificant probability for patients to transcend from HFpEF and HFmrEF to HFrEF within the first year of diagnosis poses a clinical challenge. Treatment decisions relying heavily on LVEF classifications in the presence of a high LVEF variability create a potential for delayed treatment.

Some limitations of the present study merit highlighting. All data from EHRs are collected on the basis of

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incidence in disease and trajectories in disease, treatment, and symptoms, which leads to more information about the sicker patients, with or without comorbidities that might affect the LVEF. This bias is handled in part by inclusion of both hospital admission and outpatient visits, where outpatient visits are likely to be more stable in their disease and symptoms. Furthermore, the data from EHRs are interval censored (ie, the exact time of a transition between LVEF categories is unknown). Several types of interval censoring categories are possible, with physician's care and patient self-selection being the most probable in this instance.[37] Current guidelines state that LVEF should be assessed only on worsening of symptoms.[3] Often in EHRs, there is a reference to the last recorded LVEF. This demonstrates the clinical practice of the last value carried forward and should not affect the transition rate because it keeps the patient in the same state, similar to if no LVEF was referenced.

Worth noting, ≈26 000 patients were excluded because of a lack of an LVEF value within the predefined time frame around their heart failure diagnosis. The clinical presentation of those patients may differ from the ones included in this study (Table S1). They were on average older, and a higher proportion were women. They had a lower frequency of guideline-directed medical treatment, and the first diagnosis of heart failure was more frequently set in primary care, compared with those with an available LVEF measurement. This probably reflects an older, more fragile population, which may not be eligible for more advanced treatment. It is also possibly an effect of the waiting period from primary care to certain examinations, which could be >90 days, because of the number of patients in primary care eligible for examination.

This large observational cohort study included data from EHRs, which allow for inclusion of every possible case of heart failure, and the unique Swedish setting with personal identification number allowed collection of all data available for every patient, with minimal loss to follow-up. The study included both hospital admissions and outpatient visits, which limits the risk of selection bias.[31] The LVEF values were collected both automatically and manually, for broad representation. Patients were linked to the nationwide cause of death registry; hence, there were complete records of mortality.

In conclusion, LVEF follows a normal distribution and has considerable variability over time in patients with heart failure. Hence, LVEF categorization of the population with heart failure into narrow categories has limited use, and the variability may impose a risk for underuse of efficient treatment. Assumptions of a patient's current LVEF should take this variability and the normal distribution of LVEF into account.

ARTICLE INFORMATION

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Disclosures

S. Gustafsson, M. Almstedt, and T. Cars are employed by Sence Research AB. Dr Sundström, M. Almstedt, and T. Cars are shareholders of Sence Research AB, an analytical company that has received funding from AstraZeneca for the assembly of this study database. Dr Bodegård holds a full-time position at AstraZeneca as an epidemiologist. Dr Sundström is a shareholder of Anagram kommunikation AB and Symptoms Europe AB, outside the present study. Dr Arefalk reports receiving speaker fees from Astra Zeneca and Boehringer Ingelheim. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S3.
Figures S1–S9.

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