Left ventricular ejection fraction digit bias and reclassification of heart failure with mildly reduced vs reduced ejection fraction based on the 2021 definition and classification of heart failure

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ABSTRACT

Aims Aims were to evaluate (1) reclassification of patients from heart failure with mildly reduced (HFmrEF) to reduced (HFrEF) ejection fraction when an EF = 40% was considered as HFrEF, (2) role of EF digit bias, ie, EF reporting favouring 5% increments; (3) outcomes in relation to missing and biased EF reports, in a large multinational HF registry.

Methods and results Of 25,154 patients in the European Society of Cardiology (ESC) HF Long-Term registry, 17% had missing EF and of those with available EF, 24% had HFpEF (EF≥50%), 21% HFmrEF (40%-49%) and 55% HFrEF (<40%) according to the 2016 ESC guidelines´classification. EF was "exactly" 40% in 7%, leading to reclassifying 34% of the HFmrEF population defined as EF = 40% to 49% to HFrEF when applying the 2021 ESC Guidelines classification (14% had HFmrEF as EF = 41% to 49% and 62% had HFrEF as EF≤40%). EF was reported as a value ending with 0 or 5 in ~37% of the population. Such potential digit bias was associated with more missing values for other characteristics and higher risk of all-cause death and HF hospitalization. Patients with missing EF had higher risk of all-cause and CV mortality, and HF hospitalization compared to those with recorded EF.

Conclusions Many patients had reported EF = 40%. This led to substantial reclassification of EF from old HFmrEF (40%-49%) to new HFrEF (≤40%). There was considerable digit bias in EF reporting and missing EF reporting, which appeared to occur not at random and may reflect less rigorous overall care and worse outcomes. (Am Heart J 2024;267:52–61.)

Left ventricular ejection fraction (EF) is used for diagnosis, classification, prognostic assessment, patient triage, and treatment selection, and remains the key entry criterion for clinical trials in heart failure (HF).[1]

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The Universal Definition and Classification of HF, a joint consensus document, proposed to classify HF according to EF with reduced EF (HFrEF) where EF is ≤40%, mildly reduced EF (HFmrEF) where EF ranges 41% to 49%, and with preserved EF (HFpEF) where EF is ≥50%, and with improved EF (HFimpEF) where EF is below 40% at a first assessment and then increases by ≥10 points to >40% at a second EF measurement.[2] This classification has also been adopted by the 2021 European Society of Cardiology (ESC) Guidelines on HF, and, as compared with the one from the previous 2016 ESC Guidelines where HFrEF and HFmrEF were defined as EF <40% and EF 40% to 49%, respectively, leads to reclassifying patients with an EF=40% from HFmrEF to HFrEF.[3,4]

This would be of little consequence if EF reporting were by an integer number, but several studies have suggested that a digit preference for an EF ending as an integer value equal to 0 or 5 (eg, 30% or 45% rather than 29% or 46%), termed digit bias,[5,6] may be common.[5] Since most epidemiological studies aiming to characterize HFrEF vs HFmrEF vs HFpEF were conducted considering EF = 40% as belonging to HFmrEF,[7] and this EF value might be frequent also due to a digit bias, the proportion of patients reclassified from HFmrEF to HFrEF may not be negligible. It is not known whether digit bias occurs at random or for practical purposes, or may occur in the context of less rigorous care.

Furthermore, HF guidelines have consistently recommended the measurement of EF in patients with HF, yet several data sources show missing EF measurement in a meaningful number of patients.[8-10] Missing EF measurements may reflect less rigorous care and one study has suggested that it is associated with worse outcomes.[11,12]

Therefore, we (1) assessed reclassification of patients from HFmrEF to HFrEF; 2) the extent of EF digit bias in 5% increments and its association with outcomes; 3) the extent of missing EF and its association with outcomes, in the EURObservational Research Programme (EORP) ESC-HF-Long Term (LT) Registry (ESC-HF-LT-R).

Methods

Data source

The ESC-HF-LT-Registry was conducted by the EORP in 33 ESC member countries including 337 centres, to study the characteristics and outcomes of patients with HF in Europe and surrounding regions between 2011 and 2018.[13] The registry enrolled in- and out-patients with HF (either pre-existing or new-onset HF) on a one-day-per-week basis. Automated electronic data checks were performed. The electronic case report form (eCRF) contains information on several patients' characteristics, clinical data, laboratory measurements, and imaging parameters collected at baseline (at hospital admission or out-patient visit) and also during in-hospital course for in-patients. Data on outcomes (hospital admissions and mortality) were assessed at approximately 12 months.

Patient management followed local diagnostic and therapeutic practices.[9] All patients provided written informed consent, and the registry was approved by local ethical review boards according to the regulations of each participating country.

The current analysis included 25,154 patients enrolled from 2011 to 2018. In hospitalized patients with variables collected at different time points, the discharge measure was used. In-patients who died during the hospitalization were excluded. For EF we used the measurement recorded as an integer percentage number by Echo-Doppler during the hospitalization (for in-patients), or linked with the out-patient visit. For the outcome analysis, only 19,080 patients with follow-up data were considered.

Study design

We retrospectively calculated the proportions of patients reclassified as HFrEF and HFmrEF when EF=40% was considered as HFrEF (new classification) rather than HFmrEF (old classification), as proposed by the new classification of HF provided by the Universal Definition of HF and the 2021 ESC Guidelines on HF.[2,3] We assessed patient characteristics of patients with EF = 40%, which were compared with those having EF <40% and EF=41% to 49% and EF = 35% to 39% and EF=41% to 45%. The risks of all-cause death, cardiovascular (CV) death, and of first HF hospitalization were calculated in HFrEF, HFmrEF, and HFpEF defined according to the 2016 vs the 2021 ESC Guidelines classification.[3]

We quantified the magnitude of the digit bias in our population by calculating the relative/absolute difference between the number of observed and expected EF values with the last digit 0 or 5 using two different estimated distributions for EF. We compared the prevalence of missing values for several patient characteristics and risk of outcomes (same as above) in those with EF reported as integer 0 or 5 (possible digit bias) vs those with EF registered as nonmultiple of 5.

We assessed patient characteristics and outcomes (same as above) of patients with vs without an EF measurement (ie, missing EF entry).

Statistical analysis

Categorical variables were presented as absolute numbers (%) and differences across groups were tested by the χ^2 test; continuous variables were presented as median [interquartile range] and differences were tested using the Kruskal-Wallis test.

In order to quantify the EF digit bias we assumed that the expected EF could follow:

1. A normal distribution with a mean EF of 38.6% (standard deviation 13.9%).

2. A fitted probability density function (kernel density estimation) with a smoothing bandwidth of 2.

The differences between the observed and expected values were thereafter calculated as absolute and relative differences.

For the outcome analyses, the index date was the date of the out-patient visit for out-patients and the date of discharge for in-patients. In in-patients, if the date of discharge was missing, the date of admission was used. In patients with missing information for the date of hospitalization, the time to hospitalization was imputed with half the time to the last follow-up. If the time to hospitalization was longer than the time to death or to last follow-up, it was set to death or last follow-up. Patients with unknown cause of death were considered to be non-CV death.

The time to event was illustrated by cumulative incidence curves. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated by Cox proportional hazards regressions to compare the crude risk of outcomes across the EF spectrum, and in patients with vs without digit bias and missing EF. Incidence rates per 100 patient-years with 95% Poisson CI were also calculated.

All analyses were performed using the R code for the data management and statistical analyses (https://github.com/KIHeartFailure/esc_efreclass). R version 4.2.1 (2020-06-22) (R Core Team 2019). The level of significance was set to 5%, 2-sided.

Results

Of 25,154 patients enrolled in the ESC-HF-LT-R, 33% were females and the median age was 68 (IQR 59-77) years. EF was missing in 17%.

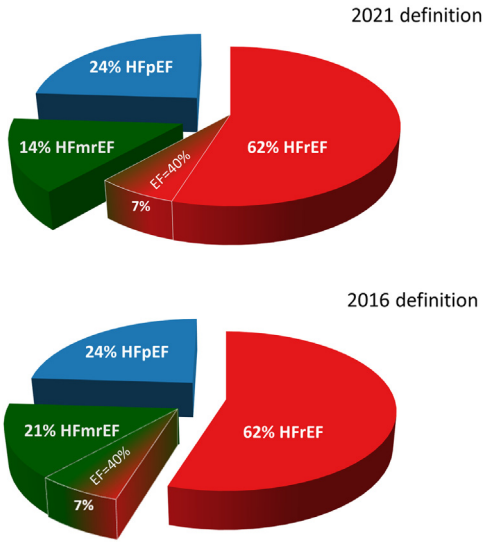
Representation of EF categories based on the different HF classifications

Of patients with available EF, 7% had EF = 40% which led to 32% of the HFmrEF subpopulation defined as EF = 40% to 49% to be reclassified as HFrEF. Therefore, based on the 2016 ESC Guidelines on HF classification 55% of patients had HFrEF (EF<40%), 21% HFmrEF (EF = 40%-49%), and 24% had HFpEF (EF≥50%), whereas according to the 2021 Guidelines HFrEF (EF≤40%), HFrEF accounted for 62% and HFmrEF (EF=41%-49%) for 14% of the population, and HFpEF still for the remaining 24% (Supplementary Figure 1, Figure 1).

The baseline characteristics of the population by EF category, where EF "exactly" = 40% was analyzed as a separate group (ie, EF<40%; EF = 40%; EF=41%-49% and EF ≥ 50%), are reported in Table. The prevalence of a EF = 40% "exactly" = 40% varied across different regions (higher in Eastern Europe and lower in Northern and Southern Europe). Patients with EF=40% were more similar to those with EF = 41% to 49% for median age, proportion of females, median body mass index (BMI), prevalence of hypertension, and HF duration (which were all higher than in EF<40%), prevalence of chronic obstructive pulmonary disease (COPD), left ventricular bundle block (LBBB), HF severity (New York Heart Association (NYHA) class and N-terminal pro B-type natriuretic peptide (NT-proBNP)), overall use medications and HF devices (which were all lower than in EF<40%). Conversely, patients with EF = 40% were more like those with EF<40% for prevalence of an ischemic HF etiology, renal disease, mitral regurgitation (which were overall higher than in EF = 41%-49%), and prevalence of atrial fibrillation (which was lower than in EF=41%-49%).

When EF = 40% as compared with EF = 36% to 39% and 41% to 44%, EF = 40% was more similar to the first for the prevalence of ischemic heart disease and history of myocardial infarction, BMI, use of loop diuretics, antiplatelets and statins (overall higher than in EF = 36%-39%) and to the latter for the prevalence of females, HF duration, COPD, depression and LBBB, use of HF devices, RASi, ivabradine and use of digoxin, (overall lower than in EF=36%-39% except for the prevalence of females). Patients with EF = 40% were overall older, with a higher prevalence of diabetes and a higher use of calcium channel blockers and antiarrhythmics. (Supplementary Table I)

Figure 1



Distribution of the heart failure with preserved, mildly reduced and reduced ejection fraction according to the 2016 and the 2021 European Society of Cardiology Guidelines on heart failure. Legend: *EF*, ejection fraction; *HFmrEF*, heart failure with mildly reduced ejection fraction; *HFpEF*, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction.

Table. Baseline characteristics by ejection fraction groups

	Variable	Missing (%)	EF <40% (HFrEF)	EF = 40%	EF = 41%-49% (HFmrEF)	EF ≥50% (HFpEF)	*P*
	N (%)		11454 (55)	1400 (7)	3030 (12)	5012 (20)	
	Hospitalized patients		4072 (36)	610 (44)	1106 (37)	2487 (50)	
	Outpatients		7382 (64)	790 (56)	1924 (63)	2525 (50)	
Demographics and socioeconomics	Regions	0					<.001
	Eastern Europe		3371 (29)	551 (39)	921 (30)	1746 (35)	
	Northern Europe		983 (9)	86 (6)	267 (9)	300 (6)	
	Southern Europe		4713 (41)	451 (32)	1155 (38)	2095 (42)	
	Western Europe		616 (5)	69 (5)	124 (4)	264 (5)	
	Middle East		398 (3)	26 (2)	50 (2)	208 (4)	
	North Africa		864 (8)	169 (12)	413 (14)	292 (6)	
	Other		509 (4)	48 (3)	100 (3)	107 (2)	
	Age, years	0	66 [57, 74]	67 [58, 76]	67 [58, 76]	72 [62, 80]	<.001
	Age categorical (≥65 y)	0	6095 (53)	803 (57)	1745 (58)	3499 (70)	<.001
	Female sex	0	2677 (23)	446 (32)	1053 (35)	2513 (50)	<.001
	Abitation status	6.9					<.001
	Home alone		1290 (12)	159 (12)	333 (12)	683 (15)	
	Home with partner		9128 (86)	1115 (86)	2406 (85)	3889 (83)	
	Nursing home		65 (1)	16 (1)	26 (1)	64 (1)	
	Other situation		156 (1)	12 (1)	55 (2)	67 (1)	
Comorbidities and risk factors	Stroke	0.1	1078 (9)	116 (8)	287 (9)	600 (12)	<.001
	Atrial fibrillation	0	4129 (36)	505 (36)	1183 (39)	2486 (50)	<.001
	Diabetes	0	3879 (34)	498 (36)	997 (33)	1630 (33)	.111
	COPD	0.2	1780 (16)	178 (13)	414 (14)	924 (18)	<.001
	Hepatic dysfunction	2.6	514 (5)	53 (4)	102 (3)	224 (5)	.037
	Thyroid dysfunction	9.1	1139 (11)	127 (10)	282 (10)	511 (11)	.518
	Depression	0.3	786 (7)	80 (6)	199 (7)	451 (9)	<.001
	Current smoking	0.5	1716 (15)	213 (15)	442 (15)	551 (11)	<.001
	Alcohol consumption	5					<.001
	Never		5468 (50)	749 (56)	1592 (56)	2848 (59)	
	Former		1426 (13)	127 (9)	273 (10)	369 (8)	
	Yes sometimes		3450 (32)	423 (31)	891 (31)	1428 (30)	
	Yes daily		495 (5)	50 (4)	98 (3)	158 (3)	
	BMI, kg/m^2	3.6	27 [25, 31]	28 [25, 31]	28 [25, 31]	28 [25, 31]	<.001
	BMI ≥ 25 kg/m^2	3.6	7826 (71)	1050 (76)	2109 (73)	3606 (74)	<.001
	Hypertension	0.2	6607 (58)	892 (64)	1907 (63)	3594 (72)	<.001
	Myocardial infarction	0.2	5627 (49)	753 (54)	1396 (46)	1789 (36)	<.001
	PCI	2.6	3052 (27)	348 (25)	617 (21)	704 (14)	<.001
	CABG	0.1	1669 (15)	196 (14)	330 (11)	410 (8)	<.001
	Valvular surgery	0.1	795 (7)	100 (7)	215 (7)	547 (11)	<.001
Clinical variables and lab measurements	HF history	0.5					<.001
	No		1601 (14)	350 (25)	778 (26)	1236 (25)	
	Yes (previous hospitalization)		5366 (47)	519 (37)	1163 (39)	1893 (38)	
	Yes (no previous hospitalization)		4439 (39)	521 (37)	1072 (36)	1848 (37)	
	HF diagnosis ≥12 mo	7.6	4660 (44)	563 (43)	1165 (41)	1948 (42)	.007
	Ischemic aetiology	0.5	6101 (54)	802 (57)	1500 (50)	1763 (35)	<.001
	Diastolic BP, mm Hg	0.3	70 [64, 80]	70 [64, 80]	70 [63, 80]	70 [62, 80]	<.001
	Systolic BP, mm Hg	0.3	120 [106, 130]	120 [110, 131]	120 [110, 135]	125 [115, 140]	<.001
	LBBB	7.3	2530 (24)	165 (13)	371 (13)	366 (8)	<.001
	EF, %	0	30 [24, 35]	40 [40, 40]	45 [43, 46]	57 [53, 61]	<.001
	NYHA class	1.2					<.001
	NYHA I		1709 (15)	295 (21)	810 (27)	1322 (27)	
	NYHA II		6046 (53)	805 (58)	1606 (54)	2603 (53)	
	NYHA III		3234 (29)	273 (20)	524 (18)	924 (19)	
	NYHA IV		353 (3)	23 (2)	40 (1)	83 (2)	
	Mitral regurgitation	4.2	4882 (45)	539 (40)	984 (34)	1470 (30)	<.001
	Aortic stenosis	4.5	419 (4)	62 (5)	163 (6)	542 (11)	<.001
	Aortic regurgitation	4.6	637 (6)	98 (7)	216 (8)	454 (9)	<.001

(continued on next page)

Table. (*continued*)

	Variable	Missing (%)	EF <40% (HFrEF)	EF = 40%	EF = 41%-49% (HFmrEF)	EF ≥50% (HFpEF)	*P*
	Tricuspid rigurgitation	4.6	2873 (26)	296 (22)	598 (21)	1241 (26)	<.001
	NT-proBNP, pg/mL	68.6	1240 [472, 3352]	748 [255, 2235]	720 [247, 2016]	675 [233, 1896]	<.001
	K^+, mEq/L	15.1	4 [4, 5]	4 [4, 5]	4 [4, 5]	4 [4, 5]	<.001
	eGFR (CKDEpi), mL/min/1.73 m^2	16.2	64 [46, 83]	63 [46, 83]	66 [48, 85]	62 [44, 80]	<.001
	Hemoglobin, g/dL	16.8	13 [12, 15]	13 [12, 14]	13 [12, 14]	13 [11, 14]	<.001
Physical signs	Rales	3.3	1427 (13)	191 (14)	375 (13)	750 (15)	<.001
	S3 Gallop	3.8	871 (8)	96 (7)	163 (6)	227 (5)	<.001
	JVP (≥6 cm)	5.4	1204 (11)	109 (8)	253 (9)	402 (8)	<.001
	Hypoperfusion	3.5	322 (3)	27 (2)	75 (3)	184 (4)	.001
	Pleural effusion	3.6	552 (5)	68 (5)	94 (3)	254 (5)	<.001
	Hepatomegaly	3.3	1267 (11)	108 (8)	232 (8)	398 (8)	<.001
	Peripheral oedema	3.1	1883 (17)	233 (17)	463 (16)	887 (18)	.065
Treatments	Loop diuretics	0	9445 (82)	1060 (76)	2095 (69)	3527 (70)	<.001
	MRA	0	8061 (70)	850 (61)	1632 (54)	1899 (38)	<.001
	RASi/ARNI	0.1	10084 (88)	1223 (87)	2622 (87)	3789 (76)	<.001
	ARNi	92.1	128 (14)	6 (7)	13 (5)	4 (1)	<.001
	Beta-blockers	0	10310 (90)	1215 (87)	2567 (85)	3733 (75)	<.001
	CCb	2.5	793 (7)	201 (14)	438 (15)	1160 (24)	<.001
	Nitrates	2.5	2270 (20)	331 (24)	688 (24)	924 (19)	<.001
	Ivabradine	2.5	1014 (9)	92 (7)	189 (6)	140 (3)	<.001
	Digoxin	0.1	2825 (25)	241 (17)	536 (18)	875 (17)	<.001
	Amiodarone	2.1	2000 (18)	191 (14)	328 (11)	486 (10)	<.001
	Antiarrhytmics	2.5	295 (3)	48 (3)	62 (2)	172 (3)	.001
	Antiplatelets	0	6476 (57)	853 (61)	1711 (56)	2347 (47)	<.001
	Anticoagulants	0	5054 (44)	527 (38)	1210 (40)	2337 (47)	<.001
	Statins	0	7204 (63)	914 (65)	1853 (61)	2702 (54)	<.001
	ICD	3.3	2899 (26)	117 (8)	257 (9)	181 (4)	<.001
	CRT	3.4	1531 (14)	87 (6)	149 (5)	117 (2)	<.001

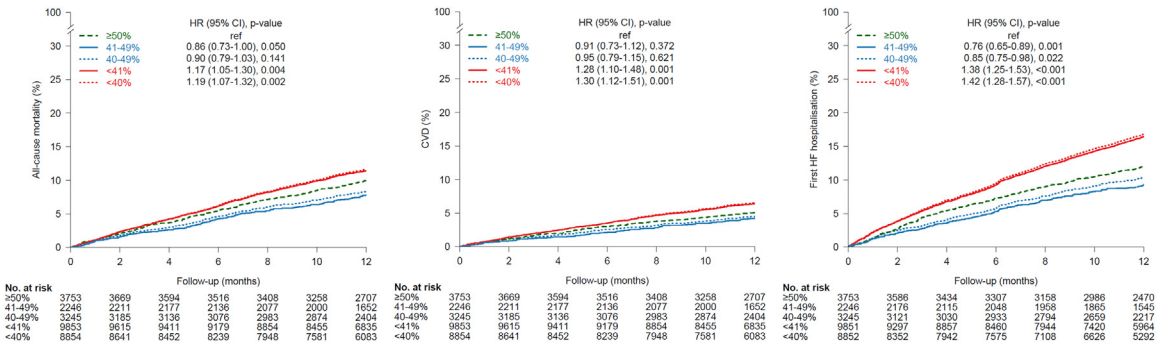
Categorical variables are presented with number (n) (percentage (%)) and continuous variables with median [first and third quartile].
ARNi, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CCb, calcium channel blockers; CDKEpi, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejaction fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HF with reduced EF (HFrEF); HF with mildly reduced EF (HFmrEF); HF with preserved EF (HFpEF); K, potassium; ICD, implantable cardioverter defibrillator; JVP, jugular venous pulse; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RASi, renin-angiotensin system inhibitors; S3, third heart sound.

Over a median follow-up of 12 (0.0-43) months, regardless of the definition of HFrEF/HFmrEF based on the different inclusion of EF = 40%, the risk of all the outcomes, ie, all-cause and CV death, and first HF hospitalization, was higher in HFrEF as compared with HFpEF, although the inclusion of EF = 40% within HFrEF led to a slight decrease in the risk difference (2%-4%). Compared with HFpEF, HFmrEF was associated with lower risk of HF hospitalization regardless of the definition, although including EF = 40% within HFrEF led to a 9% decrease in risk difference. There was no statistically significant difference in risk of all-cause and CV mortality between HFpEF and HFmrEF regardless of the HFmrEF definition, although the hazard ratios for HFmrEF were always <1.0, and the difference in risk was 4% smaller whether EF=40% was not included within HFmrEF (but rather in HFrEF) (Figure 2).

Digit bias

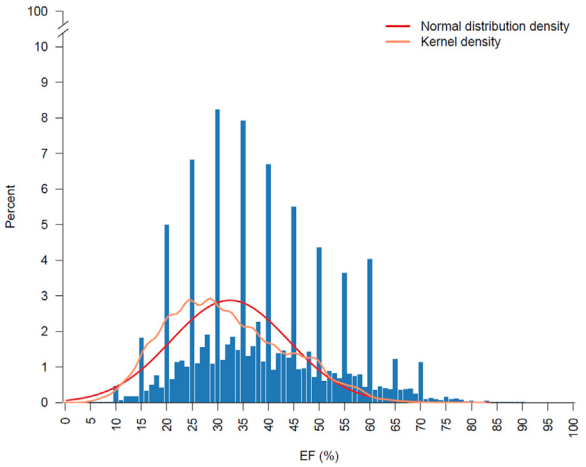
The extent of digit bias was considerable, with a relative difference between observed and expected (according to a hypothetical normal distribution) number of EF measurements with last digit equal to 0 or 5 ranging from 35% for an EF = 10%, ie, we observed 35% more EF = 10% measurements than expected according to a normal distribution, to 358% for EF = 60%, ie, measurements reporting an EF = 60% were ~3.6-fold more than expected (Figure 3). The number of measurements with an EF = 40% was overestimated by 34%. Overall, we estimated that EF was approximated to a value ending with 0 or 5 (ie, digit bias) in ~37% of the population. Results for specific EF values across the EF spectrum and with expected EF calculated according to whether EF had followed a normal distribution or the Kernel density estimate respectively are reported in Supplementary Table II. Regional differences in the prevalence of reporting EF

Figure 2



Cumulative incidence curves for all-cause mortality A, cardiovascular death B, heart failure hospitalization C, by ejection fraction subtype. Legend: *CI*, confidence intervals, *CVD*, cardiovascular death; *HR*, hazard ratio; *HF*, heart failure.

Figure 3



Observed and estimated ejection fraction values based on normal distribution and kernel density estimate. Legend: *EF*, ejection fraction. histogram = observed proportion of EF values, curves = expected proportion of EF values based on different distributions.

with last digit equal to 0 or 5 were observed. Eastern and Northern Europe regions had a higher proportion of EF last digit equal to 0 or 5 while Southern Europe and Northern African region had less.

Patients with 0 or 5 as last EF digit were more likely older, hypertensive, with atrial fibrillation, diabetes, COPD, and liver disease, had more severe HF (higher NYHA class and NT-proBNP), lower EF and renal function, and were less likely to receive HF pharmacological and device treatments as compared with those with an EF not ending with 0 or 5 (Supplementary Table III). They were also overall more likely to have missing data/assessment for symptoms and signs of HF (eg, NYHA class, rales, third heart sound (S3) gallop, jugular venous pressure (JVP), peripheral edema) and detailed echocardiographic parameters (Supplementary Table IV). They had an 11% higher risk of all-cause death (HR 1.11; 95% CI: 1.01-1.21) and HF hospitalization (HR 1.11; 95% CI: 1.03-1.21) as compared with those with an EF not ending with 0 or 5 although there were no statistically significant differences in risk of CV death (HR 1.08; 95% CI: 0.96-1.22)(Figure 4).

Missing EF assessment

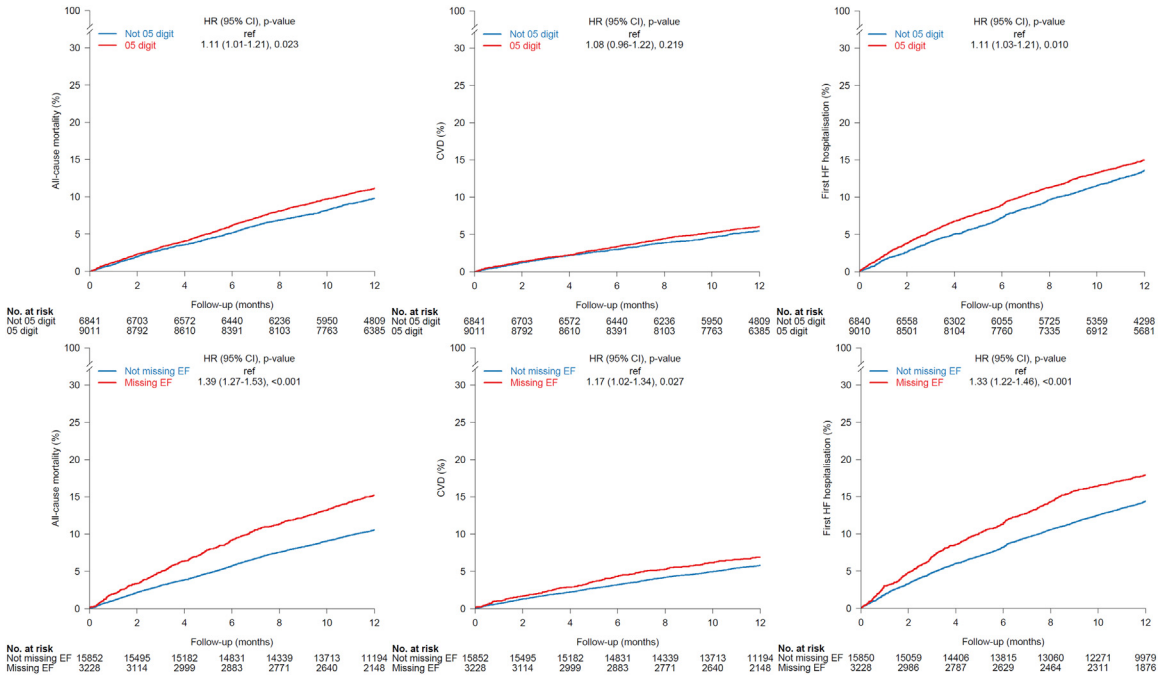
Regional differences in the prevalence of missing reported EF were observed. Eastern Europe regions had a higher proportion of missing EF while Southern Europe regions had less. Overall 17% of the population had missing EF. Patients with vs without an EF assessment were more likely older, female, with longer HF duration and an HF with ischemic etiology, had higher comorbidity burden (history of hypertension, stroke, atrial fibrillation, diabetes, COPD, renal disease, aortic stenosis), had lower NYHA class, were less likely to have JVP >6 cm or hepatomegaly but more likely to have rales or S3 gallop, were less likely to have LBBB, to receive HF pharmacological and device treatments (Supplementary Table V). They had a higher risk of all-cause (HR: 1.39; 95% CI: 1.27-1.53) and CV mortality (HR: 1.17; 95% CI: 1.02-1.34), and of HF hospitalization (HR: 1.33; 95% CI: 1.22-1.46) as compared with patients with an EF assessment (Figure 4).

Discussion

The current analysis of the ESC-HF-LT-R showed that:

1. Including EF=40% within HFrEF rather than HFmrEF, as recommended by the 2021 ESC Guidelines

Figure 4



Kaplan-Meier curves for all-cause mortality A, cardiovascular death B, heart failure hospitalization C, in patients with ejection fraction with last digit equal to 0 or 5 or different digit, or missing vs reported ejection fraction. Legend: *CI*, confidence intervals; *CV*, cardiovascular; *HR*, hazard ratio; *HF*, heart failure.

on HF and the Universal definition of HF, led to the reclassification of 7% of all patients with HF and 32% of patients with HFmrEF (reclassified as HFrEF), and therefore the prevalence of HFrEF, HFmrEF and HFrEF in the ESC-HF-LT-R is now estimated to be 62%, 15% and 24%, respectively;

2. EF=40% had similarities and differences with both EF<40% and EF=41% to 49%, which were consistent with the distribution in patient characteristics generally observed across the EF continuum;
3. Digit bias, ie, reporting an integer (0 or 5) last EF digit rather than the actual integer EF, was estimated to be observed in 37% of the population, was associated with higher comorbidity burden, less likelihood of receiving HF treatments, higher proportion of missing data (or missed evaluation) for several patient characteristics, and associated with higher morbidity/mortality;
4. About 17% of the population had missing EF measurement, which was associated with older age, female sex, higher comorbidity burden, less symptomatic HF, less likely HF treatment, and higher risk of morbidity/mortality.

EF measurement is prone to intra /interobserver variability and might vary based on the specific imaging modality used for the assessment.[14,15] Although the application of cut-offs to classify HF into HFpEF, HFmrEF, and HFrEF might seem arbitrary and an oversimplification, it is very helpful for trial inclusion, treatment selection, and guidelines recommendations, and despite all the criticism, continues to be used in clinical practice and trial design.[1,16]

The Universal Definition of HF and the 2021 ESC Guidelines HF have recently led to reclassifying patients with an EF = 40% from HFmrEF to HFrEF.[2] It is reasonable to suggest a "more inclusive" HFrEF subtype for several reasons: (1) EF<40% and EF = 40% to 49% have been shown to be overall similar in terms of patient characteristics, HF etiology and treatment response, which led to a renaming from HF with mid-range EF to HF with mildly reduced EF[7]; (2) if HFmrEF includes EF = 40%, a not negligible proportion of patients with EF<40% might be classified as HFmrEF rather than HFrEF, with weaker or nonexistent recommendations for HF therapy.[3] Our analysis showed regional differences for missing EF, digit bias and EF = 40%. For example, Eastern Europe regions

had higher proportion of reported EF with last digit 0 or 5 and therefore also EF = 40%, whereas this was less likely seen in Southern Europe regions, and not observed for the other regions. On ther other hand, EF seemed to be more likely missing in Southern Europe regions. These results should be considered and further studied since they might reflect regional differences based on the quality of clinical data acquisition and research. In our analysis, ~7% of the population had EF = 40% and therefore as many as 32% of the HFmrEF (EF = 40%-49%) group was reclassified to HFrEF. We showed that the number of patients with EF = 40% may be overestimated by ~1.3-fold due to digit bias, ie, preference of reporting an integer (0 or 5) last EF digit rather than the actual EF. Patient characteristics in EF = 40% were overall comparable with those in EF = 36% to 39% and EF =41% to 44%, with the few identified differences being consistent with how patient characteristics vary across the EF continuum, which leads to speculate that similar proportions of patients with an EF < and >40% might have been prone to digit bias for this specific EF value. Given the decrease in mortality, especially CV mortality, associated with increasing EF observed in several analyses up to an EF = 45% to 50%,[17] as expected HFrEF defined as EF ≤40% was linked with a slightly lower risk of mortality (2%-4%) as compared with HFrEF defined as EF<40%. The difference in risk when using the 2 different definitions was more accentuated for HF hospitalization, which might be explained by EF = 40% carrying a risk of this outcome more similar to EF >40% than to EF <40%.[17]

In our study, EF was approximated to a value ending with 0 or 5 (ie, digit bias) in ~37% of the population. There may be a similar tendency to approximate clinical measurements such as blood pressure.[18-20] In the TOPCAT trial, the proportion of patients with an EF value ending with 0 or 5 was higher than those with an EF ending with other numbers.[19]

Apart from the reclassification of HFmrEF and consequences for treatment indications, there may be other important consequences of or associations with digit bias. Notably, patients with a potential digit bias were more likely to have missing data for several patient characteristics linked with their medical history, HF symptoms and signs, echocardiographic parameters, and laboratory measurements, which might mean that these information were not collected or recorded. They were more likely older, had higher comorbidity burden, more severe HF, lower EF and renal function, and were less likely to receive HF pharmacological and device treatments as compared with those with an EF not ending with 0 or 5, which translated into a higher risk of morbidity/mortality, suggesting that a lack of rigor may be associated with these and other aspects of suboptimal care, leading to a worse outcome. EF was missing in 17% of the population. Missing EF was more common in older patients, female sex, and those with higher comorbidity burden, which are patient characteristics often linked with clinical inertia,[21-23] or in those with less symptomatic HF, where measuring EF might be considered of less value since less likely linked to changes in therapies. These characteristics might also partially correspond to the typical profile of an HFpEF patient. Consequently, we observed that patients with missing EF were less likely treated with HF medications and had a further increased risk of morbidity/mortality, which might again suggesting suboptimal care. Taken together, these data might suggest that treating physicians neglecting (which might mean not reporting EF or not requesting an echocardiographic exam) or approximating the reporting and/or the measurement (whether they do also perform the echocardiographic exam) of EF might be overall less rigorous and conscious of the importance of applying guidelines' recommendations (such as eg, measuring EF in HF patients), which might impact quality of care also in other respects, and thus also adversely affect patient outcomes.

Limitations

ESC-HF-LT-R enrolled patients from cardiology departments or specialized HF units (not internal medicine or geriatric departments), and therefore generalizability of our results to different settings might be limited. This has important implications since it might be speculated that the magnitude of digit bias for or missed assessment of EF in less selected cohorts might be even higher than reported here. There was no central adjudication for clinical events, and therefore cause-specific outcomes, such as CV mortality and HF hospitalization, might be misclassified. The quality of the images and methods used to calculate the EF during the reported Echo-Doppler examination (eg, Simpson, modified Simpson, etc.) were not available and differences between regions and centers could not be ruled out.

Conclusions

Including EF = 40% within HFrEF led to the reclassification of 7% of all patients with HF and 32% of those with HFmrEF defined as EF = 40-49%. 34% of those with EF = 40% had an estimated digit bias for EF, meaning that they had an EF approximated to 40%. EF measurements ending with 0% or 5% and missing EF were associated with more missing data for other patient characteristics and greater risk of CV death and HF hospitalization. Thus, the missing or biased EF might not have been at random and may raise the hypothesis of an association with less rigorous care leading to worse outcomes.

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Author contribution

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Disclosures are reported

Disclosures

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Data availability statement

The data underlying this article cannot be shared publicly due to personal data content.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.11.008.

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