



# Heart failure in the general population and impact of the 2021 European Society of Cardiology Heart Failure Guidelines

Jan-Per Wenzel<sup>1,2†</sup> , Julius Nikorowitsch<sup>1†</sup>, Ramona bei der Kellen<sup>2</sup>, Christina Magnussen<sup>1,3</sup>, Renate Bonin-Schnabel<sup>1,3</sup>, Dirk Westermann<sup>1,3</sup>, Raphael Twerenbold<sup>1,2,4</sup>, Paulus Kirchhof<sup>1,3,5</sup>, Stefan Blankenberg<sup>1,2,3</sup> and Benedikt Schrage<sup>1,3\*</sup> 

<sup>1</sup>Department of Cardiology, University Heart and Vascular Centre Hamburg, Hamburg, Germany; <sup>2</sup>Epidemiological Study Centre, Hamburg, Germany; <sup>3</sup>German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Luebeck, Hamburg, Germany; <sup>4</sup>University Centre of Cardiovascular Science, University Heart and Vascular Centre Hamburg, Hamburg, Germany; and <sup>5</sup>Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK

## Abstract

**Aim** The diagnosis of heart failure (HF) has been refined in several steps in recent years, reflecting evolving diagnostic and therapeutic approaches. The European Society of Cardiology (ESC) recently published a modified definition of HF in the 2021 heart failure (HF) guidelines. The impact of this new diagnostic algorithm on the prevalence of HF is not known. The aim of this study was to describe the contemporary prevalence of HF in a representative, completely phenotyped sample from the general population.

**Methods and results** This analysis was conducted among 7074 participants (aged 45–78 years, 51.5% women) from the population-based *Hamburg City Health Study*. Compared with the 2016 version, HF prevalence increased with the 2021 HF guidelines from 4.31% to 4.83% (12% increase). This increase was driven by a higher number of subjects with HF with reduced/mildly-reduced ejection fraction (0.47% to 0.52%; 1.37% to 2.12%), while the number of subjects with HF with preserved ejection fraction decreased from 2.46% to 2.19%. Importantly, this did not impact the known risk factor profiles of the phenotypes. Although four drugs are recommended for all subjects with HF<sub>rEF</sub> in the new guidelines, several adjunctive therapies are recommended for dedicated cases/scenarios (e.g. <1% eligibility for ivabradine/vericiguat/devices).

**Conclusion** Heart failure remains common in a contemporary general population sample. The number of patients with HF will increase when the current diagnostic criteria are applied. This offers opportunities to initiate preventive therapies, especially in patients with HF<sub>mrEF</sub> and HF<sub>rEF</sub>.

**Keywords** 2016 ESC heart failure guidelines; 2021 ESC heart failure guidelines; HF<sub>pEF</sub>; HF<sub>rEF</sub>; Diagnosis

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\*Correspondence to: Benedikt Schrage, University Heart & Vascular Center Hamburg, Department of Cardiology, Martinistr. 52, 20246 Hamburg, Germany.

Email: b.schrage@uke.de

<sup>†</sup>These authors contributed equally to this work.

## Introduction

The prevalence of failure (HF) prevalence is increasing in ageing populations.<sup>1,2</sup> At least 26 million people are affected worldwide, making it a disease of pandemic outreach with severe medical and economic consequences.<sup>3,4</sup>

Nevertheless, most data on HF prevalence originate from older population base studies and electronic health record analyses using simple diagnostic criteria. The availability of

new, evidence-based therapies for heart failure with reduced and mildly reduced ejection fraction, and the diagnostic criteria used in the evidence-generating studies, led to newer, more precise definitions of heart failure. The most recent diagnostic approach for heart failure was published in the European Society of Cardiology (ESC) 2021 guidelines for the diagnosis and treatment of chronic heart failure.<sup>5</sup> It is unclear whether these revised diagnostic criteria change the prevalence of heart failure in contemporary populations.

Therefore, it was the aim of our study to apply the 2021 ESC HF guidelines in a representative sample from the general population and to compare the prevalence of heart failure and its subtypes to other diagnostic criteria. Thereby, we sought to provide a reliable description of prevalence, characteristics, and eligibility for treatment of the different HF phenotypes in the population.

## Methods

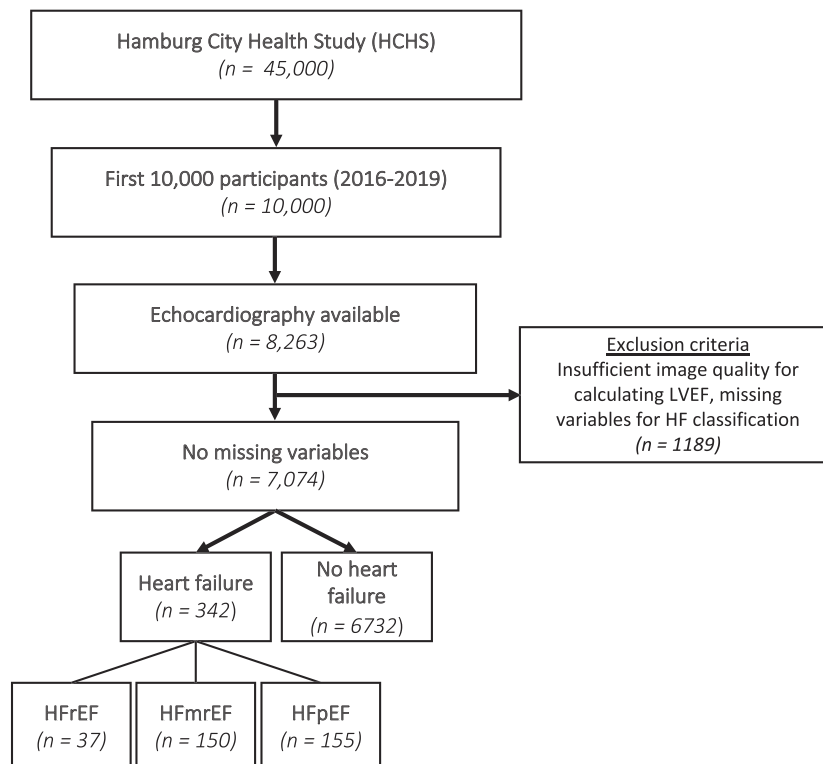
This study and the Hamburg City Health Study (HCHS, [www.uke.de/hchs](http://www.uke.de/hchs)) were conducted in agreement with the *Declaration of Helsinki*. HCHS was approved by the local ethics committee (PV5131, State of Hamburg Chamber of Medical Practitioners), and this study was approved by the review board of the HCHS. All participants provided written informed consent.

## Setting

This study was conducted within the framework of the HCHS. HCHS is an ongoing, prospective, population-based cohort study, aiming to enrol 45 000 randomly selected subjects from the metropolitan area of the city of Hamburg, Germany.<sup>6</sup> Recruitment is ongoing. All subjects are invited for a baseline study visit at the HCHS Epidemiological Study Centre at the University Medical Centre Hamburg-Eppendorf following the published HCHS protocol. The baseline visit includes a detailed clinical examination, laboratory assessment and imaging [including transthoracic echocardiography (TTE)].<sup>6</sup>

This study is based on the data from the first 10 000 subjects enrolled in HCHS between 2016 and 2019. Among these first 10 000 subjects, those with sufficient image quality for standardized assessment of cardiac function (e.g. left ventricular ejection fraction and diastolic function) and with available clinical and laboratory parameters for HF classification were considered for this study (*Figure 1*).

**Figure 1** Study PRISMA. From a total of 8263 subjects with available TTE examination, 1189 were excluded due to insufficient echocardiographic image quality or missing variables for HF classification. Following the 2021 ESC HF guidelines 342 participants were classified in the HF group. Of those, 37 were classified as HFrEF, 150 as HFmrEF, and 155 as HFpEF. ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; HCHS, Hamburg City Health Study; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; TTE, transthoracic echocardiography.



## Baseline parameters

Demographic and clinical parameters were either assessed via questionnaires (e.g. self-reported) or via standardized interviews; and all these variables were obtained based on standard operating procedures and by trained medical personnel.<sup>6</sup> Dyspnoea was evaluated by a standardized self-reported questionnaire which is provided in the supplements. Oedema were evaluated at the level of the lower leg based on physical examination by medical professionals. By applying pressure on the affected area it was checked whether pitting oedema were present. A discrimination in different grades was not performed.

All TTE examinations were performed and analysed by professional trained cardiologists and sonographers (technicians) at the baseline visit on dedicated ultrasound machines (Siemens Acuson SC2000 Prime, Siemens Healthineers, Erlangen, Germany) following standard operating procedures at the HCHS Epidemiological Study Center Hamburg-Eppendorf, Hamburg, Germany.<sup>6</sup> This included assessment of left ventricular ejection fraction and diastolic function based on two-dimensional echocardiography. Based on these exams, image analyses were performed separately on an off-line workstation. All TTE standard views were assessed in two-dimensional echocardiography, including a three-dimensional four-chamber view for chamber quantification. For continuous quality assessment, every 100<sup>th</sup> TTE exam was analysed twice by an ESC TTE certified cardiologist. Qualitative and quantitative image analyses were performed using an off-line workstation with the commercially available and established Siemens syngo SC2000 software (Siemens syngo SC 2000 Version 4.0, Siemens Healthineers, Erlangen, Germany) in agreement with the current recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).<sup>7,8</sup> Left sided volumes and ejection fraction (LVEF) were calculated from two-dimensional and three-dimensional loops using the method of disks summation. Left-sided diameters were measured in parasternal long-axis view. Mitral inflow pattern was assessed in apical four-chamber view by placing pulsed-wave (PW) Doppler sample volume between mitral leaflet tips. PW tissue Doppler imaging (TDI)  $e'$  velocity was measured in apical four-chamber view by placing the sample volume at the lateral and septal basal regions. Tricuspid annular plane systolic excursion (TAPSE) was obtained by M-mode echocardiography in the apical four-chamber view. Right ventricular fractional area change was assessed in a right ventricular focused four-chamber view.

At the baseline visit, blood was obtained from all subjects for measurement of biomarkers. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured using an immunoassay (Alere NT-proBNP for ARCHITECT, Abbott Diagnostics, IL) with a measurement range between 8.2–35 000 pg/mL.

## Heart failure classification

The HF classification was based on the recent 2021 ESC guideline on HF, and its predecessor from 2016 as a comparator (Supporting Information, *Figures S1* and *S2*), using a combination of clinical signs, echocardiographic alterations, and NT-proBNP concentrations.<sup>25</sup>

In general, HF was considered present if subjects showed symptoms/signs (e.g. dyspnoea or oedema) as well as echocardiographic criteria and/or elevated NT-proBNP.

Heart failure was then further divided into the phenotypes HFrEF, HFmrEF, and HF with preserved ejection fraction (HFpEF). When LVEF was  $<41\%$  and symptoms or signs of HF were present, subjects were classified in the HFrEF group. The combination of a LVEF of 41–49% and symptoms or signs of HF led to the classification into the HFmrEF group. Subjects were classified as having HFpEF if they presented with preserved LVEF (LVEF  $\geq 50\%$ ), symptoms or signs of HF, and either at least two or more echocardiographic signs of cardiac structural or functional abnormalities or the combination of NT-proBNP levels exceeding 125 pg/mL (sinus rhythm) or 365 pg/mL (atrial fibrillation) and at least one or more echocardiographic signs of cardiac structural or functional abnormalities. Echocardiographic signs of cardiac structural or functional abnormalities were defined as: left ventricular hypertrophy: LV mass indexed to body surface area (BSA)  $\geq 95$  g/m<sup>2</sup> for women,  $\geq 115$  g/m<sup>2</sup> for men, left atrial enlargement: defined as left atrial volume index  $>34$  mL/m<sup>2</sup> (sinus rhythm) and  $>40$  mL/m<sup>2</sup> (atrial fibrillation),  $E/e'$  ratio  $>9$ , and tricuspid regurgitation velocity ( $V_{max}$ )  $> 2.8$  m/s.

Subjects without signs/symptoms were only considered as having HF if they either had a history of HF or were on guideline-directed medical therapy (GDMT). GDMT included for HFrEF and HFmrEF beta-blockers, ACE-inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRA), SGLT2 inhibitors, and loop diuretics, while for HFpEF only SGLT2 inhibitors and loop diuretics were defined as medication.

Subjects with LVEF  $<50\%$ , but no symptoms or signs of HF were considered to have asymptomatic left ventricular systolic dysfunction (ALVSD).

## Statistical analysis

Continuous variables are presented as median and interquartile range, and categorical variables are presented as absolute numbers and percentages. Subjects with missing data were excluded when calculating percentages. The concordance between the five classifications (HFrEF, HFmrEF, HFpEF, ALVSD, and no HF) was determined using Cohen's kappa coefficients and proportion of agreement. The concordance was defined as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60),

good (0.61–0.80), and optimal (0.81–1). The reclassification percentage was determined as:  $100 - \text{proportion of agreement}$ . Data analysis was performed using R version 4.0.3.

## Results

### Study cohort

Among the first 10 000 subjects enrolled into HCHS, 7074 were included in this analysis (*Figure 1*). The 7074 subjects represented a middle-aged European population with 3642 (51.5%) women, a median age of 62 (IQR: 55–69) years and a median body mass index (BMI) of 25.9 [IQR: 23.4–28.9] kg/m<sup>2</sup> (*Figure 1, Table 1*). Hypertension was present in 4339 (64.4%) subjects, 530 (8.1%) had diabetes, 431 (6.5%) coronary artery disease (CAD), and 381 (6.0%) showed atrial fibrillation (AF). The median NT-proBNP was 77.0 [IQR: 43.0–137.0] pg/mL, and the median LVEF was 58.5% [IQR: 55.6–61.9].

### Prevalence of heart failure and co-morbidities

According to the definition provided in the 2021 ESC guidelines on acute and chronic heart failure,<sup>5</sup> 342 (4.8%) subjects were diagnosed with HF (*Figure 2*). Among those, 37 (10.8%) had HFrEF, 150 (43.9%) HFmrEF, and 155 (45.3%) HFpEF; 79 (1.1%) of the study population had ALVSD. We observed major sex differences across the HF phenotypes, with only five (13.5%) female subjects were diagnosed with HFrEF, but 40 (26.7%) with HFmrEF and 80 (52.9%) with HFpEF (*Figure 3*). Arterial hypertension was present in most subjects with HF, irrespective of the underlying HF phenotype (92.9% in HFpEF, 94.4% in HFmrEF 97.3% in HFrEF). Obesity was most common among subjects with HFpEF (64 subjects, 41.6%). Seventy-seven (24.1%) subjects with HF had diabetes, with only little variation between the HF phenotypes (25.5% in HFpEF, 22.6% in HFmrEF 26.5% in HFrEF). Atrial fibrillation was most prevalent among those with HFrEF (11 subjects, 33.3%), and the lowest prevalence was observed among those with HFmrEF (33 subjects, 24.1%). Subjects classified as HFrEF had the highest burden of CAD (19 subjects, 67.9%), moderate to severe mitral regurgitation (six subjects, 16.7%), aortic stenosis (three subjects, 9.7%), and aortic regurgitation (five subjects, 14.3%). Additionally, left bundle branch blocks were most common among HFrEF Subjects (41.9% vs. 10.6% in HFmrEF and 15.1% in HFpEF). HFpEF on the other hand was linked with the highest prevalence of chronic obstructive pulmonary disease (32 subjects, 23.7%), obstructive sleep apnoea syndrome (OSAS) (22 subjects, 16.1%), and peripheral artery disease (17 subjects, 11.7%). The highest NT-proBNP levels with a median of 637 [IQR: 239.5–1638.5] pg/mL were measured in subjects with HFrEF,

whereas those with HFmrEF had the lowest NT-proBNP levels with 189.0 [IQR: 80.0–460.2] pg/mL. NT-proBNP levels in subjects with HFpEF were 280.5 [IQR: 161.5–616.2] pg/mL. Accordingly, subjects with HFmrEF demonstrated the lowest levels of left ventricular hypertrophy with a median left ventricular mass index of 100.6 [IQR: 82.6–121.1] g/m<sup>2</sup> (125.6 [IQR: 95.8–147.2] g/m<sup>2</sup> in HFrEF and 111.4 [IQR: 97.6–128.8] g/m<sup>2</sup> in HFpEF) and few echocardiographic signs of diastolic dysfunction, for example, left atrial volume index (28.3 [IQR: 22.7–36.5] mL/m<sup>2</sup> vs. 35.0 mL/m<sup>2</sup> [IQR: 28.0–45.0] mL/m<sup>2</sup> in HFrEF and 38.5 [IQR: 32.3–46.1] mL/m<sup>2</sup> in HFpEF) and E/e' (7.7 [IQR: 6.6–10.0] vs. E/e' (8.8 [IQR: 7.0–11.0] in HFrEF and E/e' (8.8 [IQR: 7.3–11.2] in HFpEF).

### Comparison of the 2016 and 2021 European Society of Cardiology Heart Failure Guidelines on acute and chronic heart failure

The application of the 2021 ESC HF guidelines led to a 12% net increase in HF prevalence from 4.31% according to the 2016 guidelines to 4.83% (*Figure 4*). Nevertheless, the proportion of the different HF phenotypes relevantly changed. There was a sharp increase of HFmrEF prevalence from 1.38% to 2.12% (54% increase) and a minor increase of HFrEF prevalence from 0.47% to 0.52%, while the amount of HFpEF subjects declined from 2.46% to 2.19% (*Table 2*).

The extension of LVEF range from below 40% to below 41% for the HFrEF group resulted in a slight increase in HFrEF prevalence (five subjects were reclassified in the HFrEF group due LVEF between 40% and 41%). HFmrEF prevalence increased exclusively due to the inclusion of subjects without elevated NT-proBNP (56 subjects showed an LVEF of 41–50% without NT-proBNP levels >125 pg/mL). The decline of HFpEF prevalence was driven by several aspects that were changed in the 2021 ESC HF guidelines: (i) the redefinition of echocardiographic criteria for diastolic dysfunction (26 subjects met the 2016 but not the 2021 criteria for diastolic dysfunction); (ii) the new NT-proBNP limit for subjects with AF (11 subjects with AF had NT-proBNP levels <365 pg/mL); (iii) the raised LAVI threshold for subjects with AF (eight subjects suffered from AF but showed LAVI <40 mL/m<sup>2</sup>). Nevertheless, known risk factor profiles of the different phenotypes remained unchanged.

### Eligibility for guideline-recommended heart failure therapies

The new 2021 ESC HF guidelines recommend four key therapeutic drugs for all subjects with HFrEF: beta-blockers, renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors (ACEi); angiotensin receptor blockers (ARBs), and angiotensin-receptor neprilysin inhibitors (ARNIs), miner-

Table 1 Baseline characteristics of the study population

n (%)	All 7074	No HF 6653	ALVSD 79	HFHF 37	HFmEF 150	HFpEF 155
<b>Demographics + biometrics</b>						
Age, years	62 [55, 69]	62 [55, 69]	61 [54, 70]	69 [65, 74]	69 [63, 73]	70 [65, 73]
Female	3642 (51.5)	3489 (52.4)	26 (32.9)	5 (13.5)	40 (26.7)	82 (52.9)
White ethnicity	6949 (98.9)	6535 (98.9)	76 (96.2)	35 (97.2)	149 (99.3)	154 (99.4)
Black ethnicity	27 (0.4)	25 (0.4)	1 (1.3)	0 (0)	0 (0)	1 (0.6)
Asian ethnicity	50 (0.7)	46 (0.7)	2 (2.5)	1 (2.8)	1 (0.7)	0 (0)
BMI, kg/m <sup>2</sup>	25.9 [23.4, 28.9]	25.8 [23.4, 28.7]	25.9 [23.5, 29.4]	26.8 [24.7, 29.4]	28.1 [25.6, 31.9]	28.6 [24.7, 32.7]
SBP, mmHg	136.5 [124.5, 149.8]	136.5 [124.5, 149.5]	135.2 [126.5, 152.1]	128.5 [119.8, 139.2]	140.5 [132.0, 152.0]	144.0 [128.2, 158.2]
DBP, mmHg	81.5 [75.5, 88.0]	81.5 [75.5, 88.0]	84.5 [78.8, 92.4]	77.5 [69.2, 84.0]	83.5 [76.5, 90.0]	79.8 [71.4, 87.6]
<b>Co-morbidities + risk factors</b>						
Hypertension	4339 (64.4)	3981 (62.9)	43 (55.1)	36 (97.3)	136 (94.4)	143 (92.9)
Diabetes	530 (8.1)	441 (7.1)	11 (14.1)	9 (25.7)	33 (22.6)	36 (25.5)
Current smoking	1413 (20.1)	1339 (20.2)	16 (20.3)	8 (22.2)	23 (15.3)	27 (17.4)
Obesity (BMI > 25 kg/m <sup>2</sup> )	1243 (18.7)	1100 (17.6)	16 (21.1)	8 (22.9)	55 (38.2)	64 (41.6)
Coronary artery disease	431 (6.5)	315 (5.0)	3 (3.8)	19 (67.9)	47 (34.3)	47 (32.9)
COPD	444 (6.9)	395 (6.5)	0 (0)	3 (10.3)	14 (10.9)	32 (23.7)
OSAS	373 (5.8)	330 (5.4)	2 (2.8)	1 (3.6)	18 (14.3)	22 (16.1)
Peripheral artery disease	206 (3.2)	174 (2.8)	4 (5.1)	2 (7.4)	9 (7.1)	17 (11.7)
History of heart failure	213 (3.0)	124 (1.9)	0 (0)	17 (50)	25 (17.4)	47 (32.0)
Dyspnoea at						
Severe physical activity	416 (6.5)	310 (5.1)	0 (0)	8 (28.6)	31 (23.7)	67 (48.6)
Mild physical activity	154 (2.4)	120 (2.0)	0 (0)	1 (3.6)	12 (9.2)	21 (15.2)
At rest	69 (1.1)	57 (0.9)	0 (0)	1 (3.6)	2 (1.5)	9 (6.5)
Oedema (lower leg)	71 (1.7)	55 (1.4)	0 (0)	2 (13.3)	3 (3.3)	11 (12.6)
Dyspnoea and oedema	15 (0.2)	12 (0.2)	0 (0)	0 (0)	1 (0.8)	2 (2.1)
E/e' > 9	1336 (20.5)	1199 (19.4)	15 (22.7)	13 (46.4)	43 (35.2)	66 (47.5)
<b>Medication + device therapy</b>						
Loop diuretics	139 (2.1)	76 (1.2)	0 (0)	9 (24.3)	14 (9.5)	40 (26.7)
Thiazide	165 (2.4)	140 (2.2)	2 (2.5)	2 (5.4)	9 (6.1)	12 (8.0)
Beta-blocker	1121 (16.6)	927 (14.6)	0 (0)	28 (75.7)	77 (52.4)	89 (59.3)
ACE inhibitors/ARBs	1391 (20.6)	1226 (19.3)	0 (0)	21 (56.8)	78 (53.1)	66 (44.0)
ARNI	3 (0)	2 (0)	0 (0)	1 (2.7)	0 (0)	0 (0)
Ivabradin	5 (0.1)	4 (0.1)	0 (0)	1 (2.7)	0 (0)	0 (0)
MRAS	48 (0.7)	26 (0.4)	0 (0)	8 (21.6)	6 (4.1)	8 (5.3)
Vericiguat	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SGLT2i	10 (0.1)	8 (0.1)	0 (0)	1 (2.7)	0 (0)	1 (0.7)
Hydralazine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Isosorbide dinitrate	3 (0)	1 (0)	0 (0)	1 (2.7)	0 (0)	1 (0.7)
Digitoxin/Digitoxin	8 (0.1)	2 (0)	0 (0)	1 (2.7)	2 (1.4)	3 (2.0)
ICD	27 (0.5)	18 (0.4)	0 (0)	2 (7.4)	6 (5.1)	1 (0.9)
Pacemaker	23 (0.4)	11 (0.2)	0 (0)	3 (9.1)	4 (2.9)	5 (3.3)
<b>Laboratories</b>						
NT-proBNP, pg/mL	77.0 [43.0, 137.0]	74.0 [42.0, 127.0]	80.0 [40.0, 166.8]	637.0 [239.5, 1638.5]	189.0 [80.0, 460.2]	280.5 [161.5, 616.2]
LDL, mg/dL	121.0 [96.0, 146.0]	122.0 [97.0, 146.0]	117.0 [97.0, 148.0]	98.0 [66.5, 118.8]	104.5 [71.8, 132.2]	105.0 [85.0, 133.2]

(Continues)



Table 1 (continued)

n (%)	All 7074	No HF 6653	ALVSD 79	HFrEF 37	HFmrEF 150	HFpEF 155
GFR, mL/min/1.73 m <sup>2</sup>	93.2 [83.9, 101.0]	93.6 [84.6, 101.3]	92.9 [83.8, 100.2]	83.6 [66.5, 89.6]	80.6 [67.7, 92.5]	86.8 [68.9, 93.5]
Haemoglobin, g/dL	14.3 [13.6, 15.1]	14.3 [13.6, 15.1]	14.7 [13.9, 15.6]	15.0 [14.4, 15.3]	14.6 [13.6, 15.4]	13.9 [13.0, 14.9]
HbA1c, %	5.5 [5.3, 5.8]	5.5 [5.3, 5.8]	5.6 [5.4, 5.8]	5.7 [5.5, 6.3]	5.8 [5.5, 6.2]	5.7 [5.4, 6.1]

Continuous variables are presented as median and interquartile range, and categorical variables are presented as absolute numbers and percentages.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; BMI, body mass index; DBP, diastolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSAS, obstructive sleep apnoea; SGLT2i, Sodium-glucose-co-transporter 2 inhibitor; SBP, systolic blood pressure.

alocorticoid receptor antagonists (MRAs), and sodium-glucose-co-transporter 2 inhibitors (SGLT inhibitors). Furthermore, there are multiple additional treatment possibilities, reflecting a tailored therapeutic approach. In the consideration of recent data, we assumed an indication for SGLT2 inhibitors for HFmrEF.<sup>9,10</sup> Figure 5 highlights the dominant role of quadruple therapy in all subjects with HFrEF and HFmrEF (up to 54.7% eligibility of subjects within the HF population, 276 out of 10 000 subjects from the general population). Other treatment options such as digoxin, vericiguat or devices apply to selected cases demonstrated by an eligibility below 1%.

The application of guideline-directed medical therapy (GDMT) within our study population reflects the guideline recommendations at the time of enrolment. Beta-blocker therapy showed the highest prevalence in subjects with HFrEF (75.7%), followed by ACE inhibitors/ARBs (56.8%), and MRAs (21.6%). Only 2.7% of subjects with HFrEF were under therapy with ARNIs and SGLT2 inhibitors. Approximately half of all subjects with HFmrEF took beta-blockers (53.1%) and/or ACE inhibitors/ARBs (53.8%). While 4.1% of the HFmrEF group took MRAs, none were under therapy with ARNIs or SGLT2 inhibitors.

Based on the recent publication of the positive EMPEROR-PRESERVED trial, we also assumed an indication for SGLT2 inhibitors in subjects with HFpEF.<sup>10</sup> This would result in SGLT2 inhibitors being the first and only treatment pillar for HFpEF.

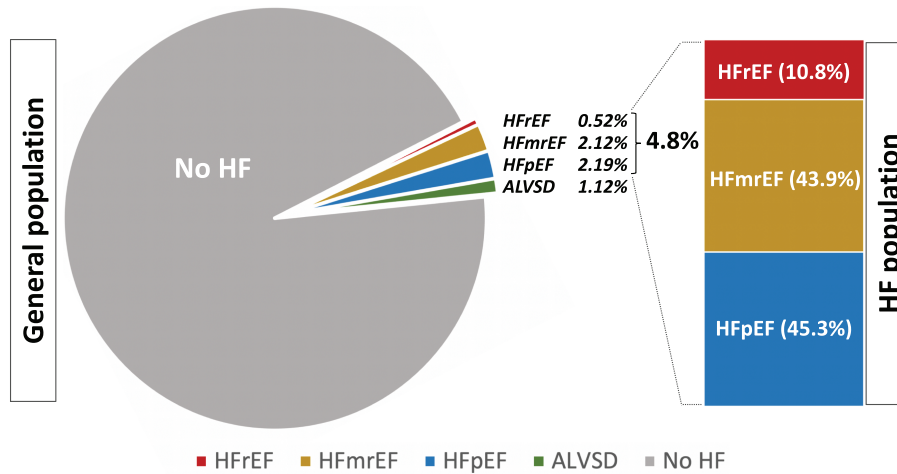
## Discussion

The prevalence of heart failure remains high in a contemporary, middle-aged population. The number of patients diagnosed with heart failure increases when contemporary diagnostic criteria are applied, reflecting a growing eligibility for evidence-based therapies in patients with HFrEF and HFmrEF.<sup>11</sup>

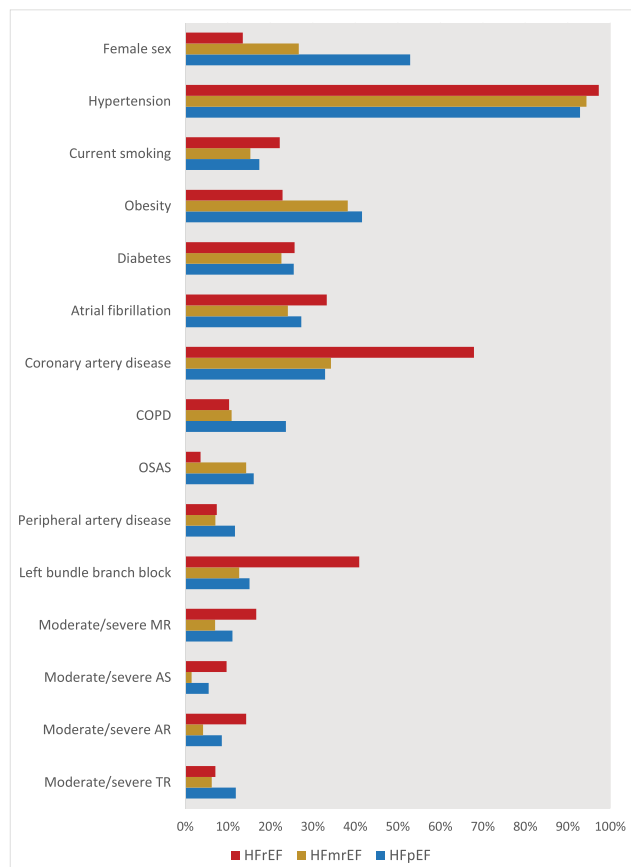
### Heart failure is very common in the general population

The prevalence of HF according to the new ESC 2021 HF guidelines was 4.8%, highlighting the relevant disease burden in the middle-aged general population. Estimates of HF prevalence derived from the ESC HF association (HFA) ATLAS study ranged from 1% to 4% with great heterogeneity across the participating countries as a result of not only diverging populations but also methodological differences.<sup>12</sup> However, HF prevalence is highly dependent on the age structure of the investigated population as HF prevalence increases with age.<sup>1,2,13</sup> Therefore, the higher HF prevalence in our cohort

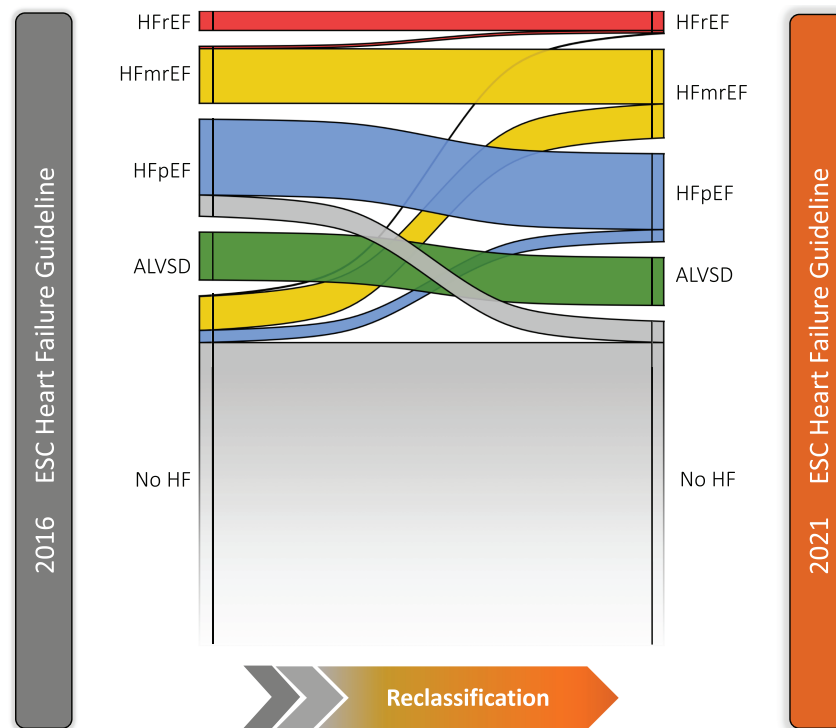
**Figure 2** Prevalence of HF in the general population as well as the distribution of the different HF phenotypes. ALVSD, asymptomatic left ventricular systolic dysfunction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



**Figure 3** HF phenotypes and their different characteristics. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; BMI, body mass index; DBP, diastolic blood pressure; DBP, diastolic blood pressure, GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSAS, obstructive sleep apnoea; SGLT2i, Sodium-glucose-co-transporter 2 inhibitor; SBP, systolic blood pressure.



**Figure 4** Reclassification of subjects into the different HF phenotypes based on the 2016 ESC vs the 2021 ESC HF guidelines. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSAS, obstructive sleep apnoea; SGLT2i, Sodium-glucose-co-transporter 2 inhibitor; SBP, systolic blood pressure.



is likely due to an exclusion of those under the age of 45 years which is in line with other studies like the Rotterdam Heart Study, which showed a median HF prevalence of 6.4% in subjects aged above 55 years (mean age 74 years).<sup>13</sup> According to most studies, HFpEF and HFmrEF versus HFrEF seem to be equally distributed among all HF patients, although these data are mainly derived from hospitalized patients.<sup>14</sup> In our study however, the prevalence of both HFmrEF and HFpEF was almost four-fold higher compared with HFrEF. These results, which are in line with recent findings in a primary care setting, might indicate a shift in prevalence from HFrEF to HFmrEF and HFpEF.<sup>15–17</sup> Importantly, the use of a standardized protocol including meticulous quality control for all echocardiography measurements in our study strongly supports this observation. Although there are strict guidelines on the measurement of LVEF, this parameter still has a high inter-observer and even intra-observer variability.<sup>7,18,19</sup> Therefore, estimates on the prevalence of HF phenotypes from studies without such a standardized protocol might be misleading, and especially “eye-balling” of LVEF might skew the estimates.<sup>20</sup>

### Increase in heart failure prevalence compared with the 2016 European Society of Cardiology Heart Failure Guidelines

The application of the ESC 2021 HF guidelines on a population level resulted in a 12% net increase in HF prevalence compared with the 2016 ESC HF guidelines. This was mainly driven by a drastic increase of 54% of HFmrEF according to the new HF guidelines. HFmrEF is redefined as a phenotype closer to HFrEF than to HFpEF, which is underpinned by renaming HFmrEF to HF with mildly reduced EF instead of mid-range EF. Redefining HFmrEF resulted in NT-proBNP and echocardiographic abnormalities beyond a mildly reduced ejection no longer being considered as diagnostic markers for HFmrEF. The removal of elevated NT-proBNP as a requirement for diagnosing HFmrEF drastically expands the HFmrEF group, offering new treatment options for this group of patients.

For diagnosing HFpEF, especially the role of NT-proBNP was partly redefined in the new HF guidelines, acknowledging the existence of a HF subgroup without elevated natriuretic

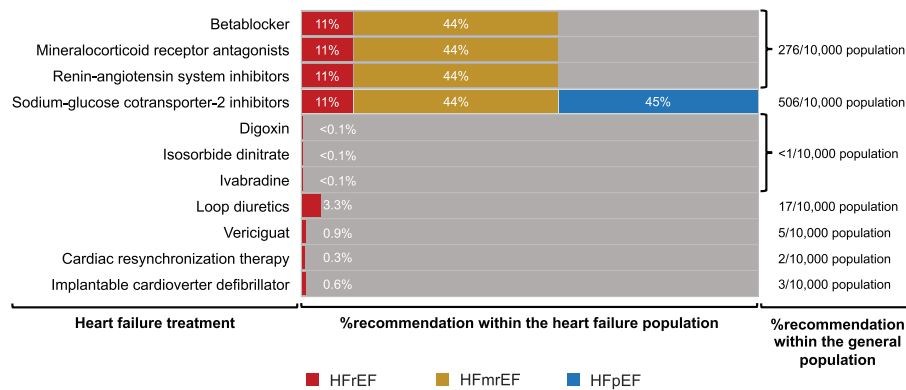


Table 2 Electrocardiographic and echocardiographic characteristic of the different HF phenotypes

n (%)	All 7074	No HF 6653	ALVSD 79	HFREF 37	HFmrEF 150	HFpEF 155
<b>ECG</b>						
Heart rate, b.p.m.	68.5 [62.0, 76.0]	68.5 [62.0, 76.0]	73.2 [65.0, 78.9]	72.0 [65.0, 83.2]	72.2 [62.5, 83.6]	69.0 [59.5, 76.0]
PR interval, ms	162.0 [148.0, 178.0]	162.0 [148.0, 178.0]	165.0 [154.0, 188.0]	168.0 [151.0, 194.5]	166.0 [148.0, 186.0]	168.0 [150.0, 184.0]
QRS interval, ms	92.0 [86.0, 100.0]	92.0 [86.0, 98.0]	94.0 [88.0, 104.0]	112.0 [100.0, 142.0]	96.0 [88.0, 108.0]	95.0 [90.0, 108.0]
QTc interval, ms	420.0 [406.0, 435.0]	419.0 [405.0, 434.0]	430.0 [416.0, 444.2]	455.5 [436.0, 485.0]	429.0 [412.0, 450.0]	430.0 [413.0, 448.0]
LBBB	290 (4.6)	235 (3.9)	5 (6.7)	13 (41.9)	14 (10.6)	23 (15.1)
RBBB	365 (5.7)	336 (5.6)	5 (6.7)	3 (9.7)	10 (7.6)	11 (7.2)
LAH	255 (4.0)	220 (3.7)	6 (8.0)	4 (12.5)	12 (9.0)	13 (8.5)
AV blocks	359 (5.1)	317 (4.8)	6 (7.5)	4 (10.8)	14 (9.3)	18 (11.8)
Atrial fibrillation	381 (6.0)	290 (4.9)	5 (6.7)	11 (33.3)	33 (24.1)	42 (27.3)
<b>Echocardiography</b>						
LVEF, %	58.5 [55.6, 61.9]	58.8 [56.0, 62.0]	47.1 [44.3, 48.8]	37.3 [29.2, 38.7]	47.7 [45.0, 49.0]	57.6 [55.2, 59.9]
LV mass index, g/m <sup>2</sup>	81.4 [71.3, 94.4]	80.7 [70.8, 92.8]	87.5 [75.6, 107.9]	125.6 [95.8, 147.2]	100.6 [82.6, 121.1]	111.4 [97.6, 128.8]
LAVI	24.9 [20.2, 30.1]	24.7 [20.0, 29.6]	21.6 [17.8, 30.1]	35.0 [28.0, 45.0]	28.3 [22.7, 36.5]	38.5 [32.3, 46.1]
LVEDV, mL	109.1 [91.2, 131.2]	108.7 [91.1, 130.5]	114.5 [90.7, 138.6]	150.2 [115.2, 247.0]	113.0 [94.7, 150.7]	116.7 [95.4, 151.8]
LV lateral w, mm/s	10.3 [8.4, 12.3]	10.3 [8.5, 12.4]	9.2 [7.3, 11.3]	8.0 [6.1, 10.7]	8.6 [6.8, 11.2]	9.7 [7.8, 11.4]
LV septal w, mm/s	8.5 [7.0, 10.2]	8.5 [7.1, 10.2]	7.6 [6.4, 9.7]	7.0 [5.5, 8.1]	7.1 [5.9, 9.1]	7.5 [6.0, 9.1]
E/e' mean ratio	7.3 [6.2, 8.6]	7.2 [6.2, 8.6]	7.8 [6.4, 9.0]	8.8 [7.0, 11.0]	7.7 [6.6, 10.0]	8.8 [7.3, 11.2]
E/A ratio	0.9 [0.8, 1.2]	0.9 [0.8, 1.2]	0.8 [0.7, 1.0]	0.7 [0.6, 0.9]	0.8 [0.6, 1.1]	0.9 [0.7, 1.2]
TR V <sub>max</sub> , m/s	2.3 [2.2, 2.5]	2.3 [2.2, 2.5]	2.3 [2.2, 2.6]	2.6 [2.3, 2.9]	2.4 [2.2, 2.6]	2.6 [2.3, 2.8]
TAPSE, mm	24.0 [21.3, 27.0]	24.2 [21.5, 27.0]	22.7 [19.9, 25.1]	20.8 [16.2, 23.8]	22.6 [19.5, 25.9]	22.8 [19.9, 26.0]
Diastolic dysfunction	623 (9.8)	323 (5.4)	79 (100.0)	37 (100.0)	150 (100.0)	34 (25.2)
AS, moderate/severe	50 (0.8)	36 (0.6)	1 (1.6)	3 (9.7)	2 (1.5)	8 (5.5)
AR, moderate/severe	197 (2.9)	173 (2.7)	0 (0)	5 (14.3)	6 (4.2)	13 (8.6)
MR, moderate/severe	134 (2.0)	97 (1.5)	4 (5.6)	6 (16.7)	10 (7.0)	17 (11.1)
TR, moderate/severe	165 (2.6)	136 (2.3)	1 (1.6)	2 (7.1)	8 (6.2)	18 (11.9)

AR, aortic regurgitation; AS, aortic stenosis; AV, atrioventricular; LAH, left anterior haemiblock; LAVI, left atrial volume index; LBB, left bundle branch block; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral regurgitation; MS, mitral stenosis; RBBB, right bundle branch block; RV, right ventricle; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation.

**Figure 5** Percentage of recommendations for guideline directed therapy within the HF population and the general population. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; BMI, body mass index; DBP, diastolic blood pressure; DBP, diastolic blood pressure, GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSAS, obstructive sleep apnoea; SGLT2i, Sodium-glucose-cotransporter 2 inhibitor; SBP, systolic blood pressure.



peptides on the one hand and demanding higher NT-proBNP thresholds for patients with AF.<sup>21,22</sup> However, several echocardiographic criteria both in subjects with and without elevated natriuretic peptides need to be fulfilled for diagnosing HFpEF, representing a simplified approach based on the recently published HFA-PEFF diagnostic algorithm.<sup>23</sup> Consequently, HFpEF was more strictly diagnosed according to the new HF guidelines compared with the 2016 HF guidelines, resulting in less cases and suggesting a more valid definition. For diagnosing HFpEF, especially the role of NT-proBNP was partly redefined in the new HF guidelines, acknowledging the existence of a HF subgroup without elevated natriuretic peptides on the one hand and demanding higher NT-proBNP thresholds for patients with AF.<sup>21,22</sup>

### Quadruple medication as a new cornerstone for heart failure therapy

The 2021 HF guidelines advocate the use of beta-blockers, MRAs, renin-angiotensin system inhibitors, and SGLT2 inhibitors in all subjects with HF rEF. Assuming an indication for HFm rEF,<sup>9,10</sup> this would translate into 276 out of 10 000 people in the middle-aged general population being eligible for this quadruple therapy compared with 47 out of 10 000 people according to the 2016 guidelines. This massive rise in eligibility is owed to the fact that beta-blockers, MRAs, and renin-angiotensin system inhibitors are no longer recommended for HF rEF subjects alone but may also be considered for those with HFm rEF.<sup>5</sup> However, these guideline recommendations were not derived from focused randomized controlled trials in HFm rEF patients but were partly based on subgroup analyses of trials including patients with LVEF >40%.

SGLT2 inhibitors are not yet medically approved nor recommended for HFm rEF and HFpEF, but it can be expected that they will be recommended for both entities based on recent data: The recently published Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR Preserved) trial demonstrated a reduction of the primary endpoint cardiovascular death or hospitalization for heart failure in HFm rEF and HFpEF subjects treated with Empagliflozin.<sup>10</sup> Especially if the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial produces similar results for Dapagliflozin, the role for SGLT2 inhibitors in HFm rEF and HFpEF will be strengthened.<sup>9,24</sup> This might almost double the number of patients eligible for SGLT2 inhibitors in the middle-aged general population.

Aside from the aforementioned medical therapy, the current guidelines suggest several adjunctive therapies such as cardiac implantable devices or drugs such as ivabradine and vericiguat for selected scenarios. This further highlights the tailored treatment approach of the 2021 ESC HF guidelines, which allows for optimization based on the patient's clinical profile, providing multiple options to improve outcomes.

### Limitations

Because most of the subjects in this study are of Caucasian ascend and as all live in the city of Hamburg, the applicability of our results to other populations might be limited. Nevertheless, it is still highly likely that our study cohort is well representative of the European/North European population. In this study we generated a diagnostic algorithm that reflects the 2021 ESC HF Guidelines as close as possible. Nevertheless, due to necessary standardizations and without

individual assessment of heart failure suspicion in each subject by a medical professional, this algorithm might lead to over- or underdiagnosing heart failure. On top of structural changes and elevated NTproBNP, this study used prescription of guideline-directed heart failure therapy to diagnose heart failure in asymptomatic patients. This allows for the inclusion of heart failure patients who are asymptomatic because of the prescribed guideline-directed heart failure therapy. However, it might also lead to an overestimation of the heart failure prevalence, as these medications might have been prescribed for other diseases than heart failure. Additionally, some measures (e.g. dyspnoea) were not assessed by clinical tests but by self-reported questionnaires, which might lead to inaccuracy in reporting. Also, there was no gold-standard for diagnosing the different HF entities. Especially for HFpEF invasive measurements are recommended, which were not applied in our study; and adding those invasive measures would further refine the classification of the study subjects.

## Conclusions

In this study, using the definition provided by the recently published 2021 ESC HF guidelines, the HF prevalence in the middle-aged general population was high (4.8%). Compared with the 2016 ESC HF guidelines, HF prevalence increased by 12%. HFmrEF was redefined by the 2021 HF guidelines with a 54% increase in prevalence, whereas the proportion of subjects with HFpEF decreased suggesting a more valid definition. The rise in HF prevalence, especially for HFmrEF, offers new possibilities to initiate preventive treatments as the new guidelines propose quadruple therapy as well as several options for adjunctive therapies personalized to the patient, highlighting a tailored treatment approach.

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## Conflict of interest

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## Supporting information

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

**Figure S1.** Flow chart of the 2021 ESC HF classification. HxHF = history of heart failure; All other abbreviations as in Table 1.

**Figure S2.** Flow chart of the 2016 ESC HF classification. HxHF = history of heart failure; All other abbreviations as in Table 1.

**Table S1.** Reclassification table of HF prevalence using the 2021 ESC HF algorithm and the 2016 ESC HF algorithm. Subjects for whom at least one classification could not be determined (1220) were excluded. Abbreviations as in Table 1.

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