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Original article

Temporal trends in characteristics, treatment, and outcomes of heart failure in octogenarians over two decades

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ABSTRACT

Introduction and objectives: Octogenarians represent the most rapidly expanding population segment in Europe. The prevalence of heart failure (HF) in this group exceeds 10%. We assessed changes in clinical characteristics, therapy, and 1-year outcomes over 2 decades in chronic HF outpatients aged ≥ 80 years enrolled in a nationwide cardiology registry.

Methods: We included 2520 octogenarians with baseline echocardiographic ejection fraction measurements and available 1-year follow-up, who were recruited at 138 HF outpatient clinics (21% of national hospitals with cardiology units), across 3 enrolment periods (1999-2005, 2006-2011, 2012-2018).

Results: At recruitment, over the 3 study periods, there was an increase in age, body mass index, ejection fraction, the prevalence of obesity, diabetes, dyslipidemia, pre-existing hypertension, and atrial fibrillation history. The proportion of patients with preserved ejection fraction rose from 19.4% to 32.7% (P for trend < .0001). Markers of advanced disease became less prevalent. Prescription of beta-blockers and mineralocorticoid receptor antagonists increased over time. During the 1-year follow-up, 308 patients died (12.2%) and 360 (14.3%) were admitted for cardiovascular causes; overall, 591 (23.5%) met the combined primary endpoint of all-cause mortality or cardiovascular hospitalization. On adjusted multivariable analysis, enrolment in 2006 to 2011 (HR, 0.70; 95%CI, 0.55-0.90; P = .004) and 2012 to 2018 (HR, 0.61; 95%CI, 0.47-0.79; P = .0002) carried a lower risk of the primary outcome than recruitment in 1999 to 2005.

Conclusions: Among octogenarians, over 2 decades, risk factor prevalence increased, management strategies improved, and survival remained stable, but the proportion hospitalized for cardiovascular causes declined. Despite increasing clinical complexity, in cardiology settings the burden of hospitalizations in the oldest old with chronic HF is declining.

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◇ See appendix of the supplementary data for the complete list of centers and investigators.

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Tendencias temporales en las características, tratamiento y resultados de la insuficiencia cardiaca en octogenarios durante dos décadas

Palabras clave:
Octogenarios
Insuficiencia cardiaca crónica
Tendencias temporales
Resultados
Polifarmacia

RESUMEN

Introducción y objetivos: Los octogenarios representan el segmento de población de más rápida expansión en Europa; la prevalencia de la insuficiencia cardiaca (IC) en este grupo supera el 10%. Se evaluaron los cambios en las características clínicas, el tratamiento y los resultados a un año durante dos décadas en pacientes ambulatorios con IC crónica de edad ≥ 80 años incluidos en un registro nacional de cardiología.
Métodos: Se incluyó a 2.520 octogenarios con mediciones de la fracción de eyección ecocardiográfica basal y seguimiento a 1 año disponibles, inscritos en 138 clínicas ambulatorias de IC (21% de los hospitales nacionales con unidades de cardiología), reclutados a lo largo de tres épocas (1999-2005, 2006-2011, 2012-2018).
Resultados: En el momento de la inclusión, a lo largo de los 3 periodos de estudio, aumentaron la edad, el índice de masa corporal, la fracción de eyección, la prevalencia de obesidad, diabetes, dislipemia, hipertensión preexistente y la historia de fibrilación auricular. La proporción de pacientes con fracción de eyección conservada aumentó del 19,4% al 32,7% (p de tendencia < 0,0001). Los marcadores de enfermedad avanzada se hicieron menos prevalentes. La prescripción de bloqueadores beta y antagonistas de los receptores de mineralocorticoides aumentó con el tiempo. Durante el seguimiento a un año, 308 pacientes fallecieron (12,2%) y 360 (14,3%) fueron ingresados por causas cardiovasculares; en total, 591 (23,5%) alcanzaron el objetivo primario combinado de mortalidad por todas las causas u hospitalización cardiovascular. Mediante un análisis multivariable ajustado, la inclusión en 2006-2011 (HR = 0,70; IC95%, 0,55-0,90; p = 0,004) y 2012-2018 (HR = 0,61; IC95%, 0,47-0,79; p = 0,0002), conllevó un menor riesgo del resultado primario que la inclusión en el periodo 1999-2005.
Conclusiones: Entre los octogenarios, a lo largo de 2 décadas, la prevalencia de los factores de riesgo aumentó, las estrategias de tratamiento mejoraron, la supervivencia se mantuvo estable, pero la proporción de hospitalizados por causas cardiovasculares disminuyó. A pesar de la creciente complejidad clínica, en el ámbito de la cardiología la carga de hospitalizaciones en los ancianos con IC crónica está disminuyendo.
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Abbreviations

GDMT: guideline-directed medical treatment
HFmrEF: heart failure with mildly reduced ejection fraction
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
LVEF: left ventricular ejection fraction

INTRODUCTION

Heart failure (HF) affects over 10% of people older than 80 years.[1] This population segment, the oldest old according to the World Health Organization definition, represents the most rapidly expanding group in Europe: the proportion of Europeans older than 80 years in 2019 (5.2%) is projected to rise to 7.2% by 2030.[2] In our country, the percentage of octogenarians grew from 4.4% to 7.6% in the last 2 decades. In the UK, patient age and multimorbidity at first presentation of HF markedly increased from 2002 to 2015.[3] In the US among octogenarians, the number of HF patients is expected to grow by 66% from 2010 to 2030.[4]

Elderly patients have a distinct HF phenotype, characterized by female preponderance, smaller ventricles, higher left ventricular ejection fraction (LVEF) values, i.e the HF with preserved ejection fraction (HFpEF) phenotype, and a higher comorbidity burden.[5–9] In recent years in the general HF population a shift from HF with reduced ejection fraction (HFrEF) toward the HFpEF phenotype[10,11] has been documented in parallel with the growth of obesity, type 2 diabetes, dyslipidemia, and hypertension, ie, the cardiometabolic risk factors that provide the breeding ground for HFpEF development.[12] Whether similar trends also occur in the oldest old HF population has not been described.

Data on evolving prognosis in this patient group are also limited. Among elderly outpatients with chronic HF,[13,14] 1-year mortality, although lower than in participants hospitalized for acute HF, still exceeds 10%,[15] with better survival in cardiology than in cross-discipline or primary care cohorts.

To address the scarcity of data on trends over time in clinical phenotype, treatment and prognosis of octogenarians with HF, we analyzed changes in the characteristics, drug and device therapy, 1-year all-cause mortality and hospitalizations in outpatients older than 80 years enrolled in a national chronic HF registry.

METHODS

Study design and setting

IN-CHF (Italian Network on Chronic Heart Failure) is a nationwide, strictly observational multicenter registry of patients with chronic HF referred to cardiology outpatient clinics that was set up in 1995 by the Working Group on Heart Failure and by the Research Center of our scientific society.[16] Standardized procedures to collect and enter data using ad hoc software were disseminated in training workshops. The protocol was approved by the Institutional Review Board of each participating center. All patients provided informed consent for scientific use of their clinical data collected in an anonymous way.

This analysis refers to patients aged ≥ 80 years with a diagnosis of chronic HF as defined in updated European Society of Cardiology guidelines,[17–21] who were recruited and followed up as outpatients at 138 HF clinics of our network. Participating units represented 21% of hospitals with cardiology units in our country,

and most (59%) were located at secondary or tertiary cardiology referral centers with coronary care units and catheterization laboratory; one fourth also had cardiac surgery facilities, and 10% were academic centers. Center distribution was 51% north, 24% center, and 25% south, with a slight unbalance with respect to our geographic population distribution (46% north, 20% center, and 34% south).

Patients could be enrolled at the first presentation to the HF outpatient clinic, irrespective of disease stage or duration. Clinical management was based on the physician's judgement.

We reviewed the clinical characteristics of patients enrolled from 1 January, 1999 to 31 May, 2018, who had baseline echocardiographic documentation of LVEF and prospective follow-up data available during the first year after enrolment.

According to the time of recruitment, we divided the study period into 3 periods, corresponding approximately to the implementation in HF management of the landmark trials on beta-blockers (1999-2005) and device therapy (2006-2011) and to the clinical development of angiotensin II receptor-neprilysin inhibitors (2012-2018), respectively.

Variables and data sources

For each patient, demographics, clinical history (including HF symptom duration and previous hospital admissions for HF), NYHA class and primary etiology of HF were entered in the database. When multiple etiologic factors were present, the one judged by the referring cardiologist to be predominant was identified as the primary cause. Ischemic etiology of HF was defined as a history of myocardial infarction, stable or unstable angina, percutaneous coronary revascularization, or coronary artery bypass grafting. Pre-existing hypertension was defined as high blood pressure values (systolic $>$ 140 mmHg or diastolic $>$ 90 mmHg) or use of antihypertensive medications prior to HF diagnosis. Patients newly diagnosed with diabetes or on oral hypoglycemic agents or insulin were defined as diabetics. Incident HF was defined as a history of HF $<$ 6 months and no admission for HF in the previous year.

HF phenotypes were classified according to LVEF values as HFrEF ($<$ 40%), HF with mildly reduced ejection fraction (HFmrEF; 40%-49%) or HFpEF ($\geq$ 50%).[21]

Laboratory findings were systematically collected from 2006 onward. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, which includes age, sex and creatinine.

HF guideline-directed medical treatment (GDMT) was defined as the daily intake of $\geq$ 3 guideline-recommended drugs, renin-angiotensin system inhibitors (RASI) (including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, angiotensin-receptor neprilysin inhibitors), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA). Prescription rates of HF-GDMT over time were compared in the overall population, in the subset of patients with HFrEF and in those with LVEF $\geq$ 40%, who had a clinical indication (pre-existing hypertension, diabetes, previous myocardial infarction) for these agents. HF-GDMT were recoded as percent of target doses[22] of RASI, BB, and MRA; patients were reclassified based on achievement of $\geq$ 50% of the target.

Non-HF polypharmacy was defined as the daily intake of $\geq$ 5 drugs, excluding from the computation GDMT drugs.[23]

Study outcomes

The primary study endpoint was all-cause mortality or hospital admission for $>$ 24 hours (ie, overnight stay) for cardiovascular causes (table 1 of the supplementary data). Although no provision was made for endpoint validation, specific training to standardize data collection was imparted at the beginning of the study. Data on admissions were obtained from hospital discharge codes and enquiries to primary care physicians.

Statistical analysis

Categorical variables are reported as number and percentages, and were compared by the chi-square test; continuous variables are expressed as means and standard deviations, and were compared by analysis of variance, if normally distributed, or the Kruskall-Wallis test, if not. Temporal trends were tested by the Cochran-Armitage test (binary variables), and by the Kendall Tau rank correction coefficient with the Jonkheere-Terpstra test (continuous variables).

Multivariable logistic regression on RASI prescription was performed including as covariates: estimated glomerular filtration rate ($<$ 30; $\geq$ 30 mL/min/1.73 m^2; unknown), hyperkalemia ($<$ 5.5; $\geq$ 5.5 mEq/lt, unknown), MRA and BB prescription, systolic blood pressure and LVEF; age and sex were not considered since they are included in the formula.

All patients were observed until the end of month 12 since enrolment or the occurrence of death. Cox multivariable analysis was performed to model the impact of enrolment period on the combined primary endpoint of all-cause death or cardiovascular hospitalization, whichever came first, and on the secondary endpoint of all-cause mortality, after adjustment for covariates that had been associated with prognosis in the previous literature. These included demographics (age, sex), history of HF (hypertensive, ischemic or other HF etiology, HF history $>$ 6 months, $\geq$ 1 HF admission previous year), comorbidities (history of atrial fibrillation, pre-existing hypertension, diabetes, previous stroke/transient ischemic attack), clinical findings (NYHA class III-IV, body mass index, systolic blood pressure, heart rate, LVEF), HF therapies (furosemide, RASI, BB, MRA, implanted cardioverter defibrillator/cardiac resynchronization therapy-defibrillator) and non-HF polypharmacy. Moreover, in a second model, guideline-recommended drugs were considered together as the binary variable HF-GDMT.

Furthermore, patients were classified based on the intake of either HF-GDMT or non-HF polypharmacy, as a 4-entry categorical variable: neither (reference group), HF-GDMT (only), non-HF polypharmacy (only), or both. Direct adjusted Kaplan-Meier curves for all-cause mortality or cardiovascular hospitalization according to the above polypharmacy variable were obtained by a stratified Cox regression analysis. The model was adjusted for the variables that were statistically significant at a previous Cox analysis with backward selection. A simultaneous P value was obtained to test the null hypothesis of no difference among the curves.

All tests were 2-sided; a P value $<$ .05 was considered statistically significant. All the analyses were performed with SAS system software, version 9.4.

RESULTS

Clinical characteristics

From 1999 to 2018, 2520 chronic HF patients aged $\geq$ 80 years were recruited in the IN-CHF Registry; 1010 (40.1%) were women. Overall, 1226 (48.7%) had HFrEF, 691 (27.4%) had HFpEF, and 603 (23.9%) had HFmrEF. As depicted in table 1, phenotype groups differed significantly in demographics and characteristics such as the prevalence of obesity, pre-existing hypertension, atrial

Table 1
Clinical characteristics, drug and device therapy, and outcomes by phenotype

	HFrEF n = 1226	HFmrEF n = 603	HFpEF n = 691	*P for trend*
Clinical characteristics				
Age, y	83 ± 3	84 ± 3	84 ± 4	< .0001
Women	377 (30.8)	239 (39.6)	394 (57.0)	< .0001
Current smoker (n = 1976)	44 (4.6)	26 (5.6)	18 (3.3)	.31
Pre-existing hypertension	770 (62.8)	428 (71.0)	533 (77.1)	< .0001
Dyslipidemia	253 (20.6)	145 (24.1)	135 (19.5)	.78
Diabetes	316 (25.8)	193 (32.0)	200 (28.9)	.07
Obesity	121 (9.9)	89 (14.8)	137 (19.8)	< .0001
Previous stroke/TIA	121 (9.9)	60 (10.0)	69 (10.0)	.93
HF history ≥ 6 mo	849 (69.3)	415 (68.8)	484 (70.0)	.76
≥ 1 HF admission, previous y	626 (51.1)	248 (41.1)	297 (43.0)	.0001
Incident HF[a]	135 (11.0)	85 (14.1)	74 (10.7)	.92
Ischemic etiology (n = 1067)	630 (51.4)	290 (48.1)	147 (21.3)	< .0001
NYHA IIII-IV, %	375 (30.6)	132 (21.9)	192 (27.8)	.07
History of atrial fibrillation	468 (38.2)	261 (43.3)	389 (56.3)	< .0001
Left bundle branch block	304 (24.8)	90 (14.9)	63 (9.1)	< .0001
GFR < 30 mL/min/1.73 m^2 (n = 1365)	107 (17.2)	45 (14.1)	44 (10.5)	.002
Body mass index	25.0 ± 3.8	25.7 ± 4.0	26.0 ± 4.4	< .0001
Systolic blood pressure, mmHg	125 ± 19	129 ± 20	130 ± 21	< .0001
Diastolic blood pressure mmHg	73 ± 10	74 ± 10	73 ± 10	.20
Heart rate bpm	72 ± 14	71 ± 13	72 ± 14	.59
eGFR mL/min/1.73 m^2 (n = 1365)	43.3 ± 14.3	46.0 ± 14.4	47.4 ± 14.9	< .0001
LVEF, %	30.5 ± 5.7	43.0 ± 2.8	57.8 ± 6.4	< .0001
Drug therapy				
Non-HF polypharmacy[b]	491 (40.1)	232 (38.5)	256 (37.1)	.19
Furosemide	1141 (93.1)	527 (87.4)	597 (86.4)	< .0001
Furosemide ≥ 75 mg/d (n = 1823)	364 (41.3)	151 (36.1)	203 (38.8)	.27
Digitalis	293 (23.9)	125 (20.7)	155 (22.4)	.36
Nitrates	371 (30.3)	163 (27.0)	150 (21.7)	< .0001
Ivabradine	48 (3.9)	26 (4.3)	8 (1.2)	.003
Oral anticoagulants	467 (38.1)	239 (39.6)	342 (49.5)	< .0001
RASI	1014 (82.7)	477 (79.1)	525 (76.0)	.0003
BB	896 (73.1)	400 (66.3)	429 (62.1)	< .0001
MRA	666 (54.3)	285 (47.3)	303 (43.9)	< .0001
RASI and BB	335 (27.3)	165 (27.4)	187 (27.1)	.91
RASI and BB and MRA	409 (33.4)	148 (24.5)	132 (19.1)	< .0001
Devices				
CRT-P	22 (1.8)	11 (1.8)	3 (0.4)	.02
CRT-D	89 (7.3)	19 (3.2)	7 (1.0)	< .0001
ICD	193 (15.7)	35 (5.8)	12 (1.7)	< .0001
1-year outcomes				
All-cause mortality	170 (13.9)	73 (12.1)	65 (9.4)	.004
All-cause death or CV hospitalization	325 (26.5)	129 (21.4)	137 (19.8)	.0005
All-cause hospitalization	294 (24.0)	113 (18.7)	122 (17.7)	.0006
Non-CV hospitalization	117 (9.5)	47 (17.8)	52 (7.5)	.11
CV hospitalization	202 (16.5)	76 (12.6)	82 (11.9)	.003
HF hospitalization	117 (9.5)	41 (6.8)	52 (7.5)	.08

BB, beta-blockers; CV, cardiovascular; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacing; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NA, not available; OAC, oral anticoagulants; RASI, renin-angiotensin system inhibitors; TIA, transient ischemic attack.
The data are expressed as No. (%) or mean ± standard deviation.
[a] Patients with no admission in the previous year, symptom onset < 6 months.
[b] Patients receiving 5 or more non-HF drugs.

Table 2
Changes in clinical characteristics over time

	1999-2005 n = 547	2006-2011 n = 659	2012-2018 n = 1314	*P for trend*
Age, y	83 ± 3	84 ± 3	84 ± 3	< .0001
Women	211 (38.6)	270 (41.0)	529 (40.3)	.59
Current smoker (n = 1976)	10 (3.1)	27 (5.7)	51 (4.3)	.72
Pre-existing hypertension	286 (52.3)	442 (67.1)	1003 (76.3)	< .0001
Dyslipidemia	54 (9.9)	131 (19.9)	348 (26.5)	< .0001
Diabetes	120 (21.9)	181 (27.5)	408 (31.1)	< .0001
Obesity	53 (9.8)	85 (13.1)	209 (16.0)	.0003
Previous stroke/TIA	53 (9.8)	69 (10.5)	128 (9.7)	.93
HF history ≥ 6 months	321 (58.7)	463 (70.3)	964 (73.4)	< .0001
≥ 1 HF admission in previous year	334 (61.1)	304 (46.1)	533 (40.6)	< .0001
Incident HF[*]	75 (13.7)	74 (11.2)	145 (11.0)	.13
Ischemic etiology (n = 1067)	250 (45.7)	292 (44.3)	525 (40.0)	.01
Ischemic, previous MI	179 (71.6)	238 (81.5)	391 (74.5)	.74
Ischemic, previous PCI	40 (16.0)	97 (33.2)	266 (50.7)	< .0001
Ischemic, previous CABG	40 (16.0)	79 (27.1)	140 (26.7)	.004
NYHA IIII-IV, %	182 (33.3)	185 (28.1)	332 (25.3)	.0005
History of atrial fibrillation %	142 (26.0)	282 (42.8)	694 (52.8)	< .0001
Left bundle branch block	101 (18.5)	122 (18.5)	234 (17.8)	.70
GFR < 30 mL/min/1.73 m^2 (n = 1365)	NA	50 (14.7)	146 (14.3)	.85
Body mass index	24.8 ± 3.6	25.4 ± 4.1	25.7 ± 4.2	< .0001
Systolic blood pressure, mmHg	134 ± 22	128 ± 20	124 ± 18	< .0001
Diastolic blood pressure, mmHg	77 ± 10	74 ± 9	71 ± 10	< .0001
Heart rate, bpm	75 ± 15	73 ± 14	70 ± 13	< .0001
eGFR mL/min/1.73 m^2 (n = 1365)	NA	45 ± 13	45 ± 15	.48
LVEF, %	38 ± 13	40 ± 12	43 ± 13	< .0001

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; HFrEF, heart failure with reduced ejection fraction; NA, not available; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. The data are expressed as No. (%) or mean ± standard deviation.

[*] Patients with no admission in the previous year and symptom onset < 6 months.

fibrillation, ischemic etiology, and kidney dysfunction. Drug therapies, specifically neurohormonal modulators, differed. Patients with HFrEF had the worst outcome rates.

Table 2 describes trends in clinical characteristics across the 3 time periods. Over time, sex distribution, smoking status, the prevalence of previous stroke/transient ischemic attack, myocardial infarction, left bundle branch block and the proportion of patients with incident HF did not change significantly. Conversely, in agreement with the observed phenotypic shift from HFrEF toward HFpEF (figure 1), mean age, body mass index, and LVEF gradually increased, while the prevalence of obesity, diabetes, dyslipidemia, pre-existing hypertension, and history of atrial fibrillation, as well as the proportion of ischemic patients who had undergone percutaneous/surgical revascularization, progressively increased across periods.

The proportion of patients with clinical markers of severe disease, including recent HF admissions and NYHA class III-IV symptoms, decreased. In recent periods, more patients had a long history of HF symptoms and lower blood pressure and heart rate values.

Drug and device therapies

Significant temporal shifts were observed (table 3) in prescribed therapies in the 3 cohorts.

Digoxin and nitrate prescription declined, while more patients were treated with furosemide and, among these, the proportion of those who received ≥ 75 mg/d showed an increasing trend. Prescription of oral anticoagulants, MRA and BB significantly rose overall, while the achievement of target GDMT doses, though on the rise, remained limited.

Notably, we found an opposite trend for RASI prescriptions and the proportion on target dose, which declined significantly in the 2012 to 2018 cohort. To explore potential reasons for this divergent trend, we performed multivariable logistic regression on RASI prescription. Among covariates detailed in Methods, RASI prescription was independently associated with kidney function (eGFR < 30 mL/min/1.73m^2, odds-ratio [OR], 0.27, 95% confidence interval [95%CI] 0.20-0.38, $P < .0001$), systolic blood pressure (OR per 5 mmHg increase 1.08; 95%CI, 1.05-1.11; $P < .0001$), LVEF (OR per 5 unit increase 0.91; 95%CI, 0.87-0.94; $P < .0001$), and MRA (OR, 0.81; 95%CI, 0.66-1.00; $P = .049$).

Prescription of HF-GDMT, and specifically RASI-BB-MRA combination therapy, was consistently higher at all time points in patients with HFrEF, when scaled to the overall cohort (table 3). The percentage on non-HF polypharmacy also rose significantly across periods.

The proportion of patients who had implanted devices at the time of enrolment reflected treatment decisions that had occurred before recruitment, hence at a younger age, and possibly earlier stage of the disease, and grew markedly across periods.

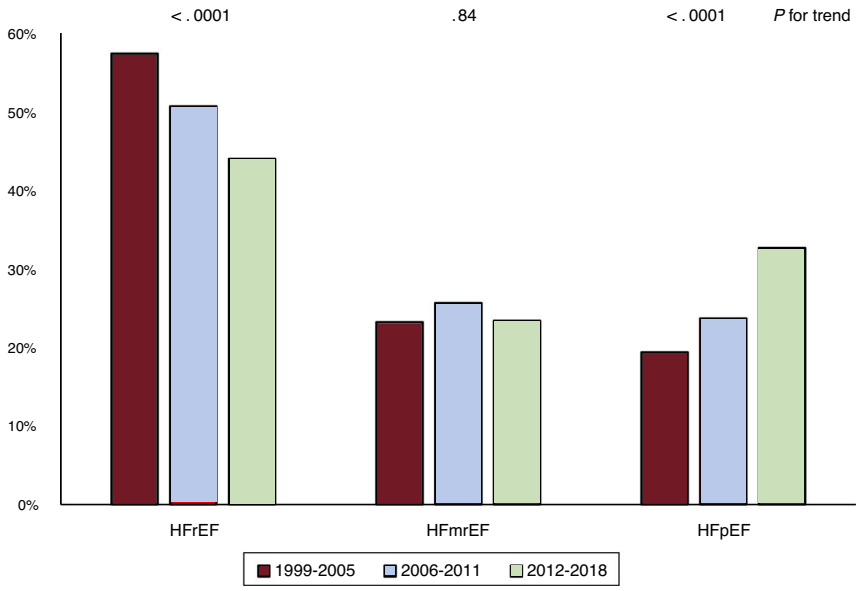

Figure 1. Phenotypic shifts over 2 decades. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Table 3
Changes in drug and device therapy over time

	1999-2005	2006-2011	2012-2018	*P for trend*
	n = 547	n = 659	n = 1314	
Drug therapy				
Non-HF polypharmacy[a]	133 (24.3)	200 (30.4)	646 (49.2)	< .0001
Furosemide	474 (86.7)	588 (89.2)	1203 (91.6)	.001
Furosemide ≥ 75 mg/d (n = 1823)	47 (27.3)	155 (34.1)	516 (43.1)	< .0001
Digitalis	244 (44.6)	168 (25.5)	161 (12.3)	< .0001
Nitrates	263 (48.1)	223 (33.8)	198 (15.1)	< .0001
Ivabradine	0 (0.0)	3 (0.5)	79 (6.0)	< .0001
Oral anticoagulants	112 (20.5)	228 (34.6)	708 (53.9)	< .0001
RASI (dose for n = 1390)	471 (86.1)	553 (83.9)	992 (75.5)	< .0001
On RASI at ≥ 50% target dose	32 (19.1)	62 (16.9)	103 (12.0)	.004
BB (dose available n = 1442)	211 (38.6)	435 (66.0)	1079 (82.1)	< .0001
On BB at ≥ 50% target dose	3 (2.9)	16 (4.8)	82 (8.2)	.007
MRA	257 (47.0)	277 (42.0)	720 (54.8)	< .0001
RASI + BB	99 (18.1)	216 (32.8)	372 (28.3)	.0004
RASI + BB + MRA	82 (15.0)	152 (23.1)	455 (34.6)	< .0001
Drug therapy Class I indication				
OAC, AF history (n = 1118)	64 (45.1)	166 (58.9)	609 (87.8)	< .0001
RASI HFrEF (n = 1226)	273 (86.9)	288 (86.2)	453 (78.4)	.0004
RASI, LVEF ≥ 40%[b] (n = 1092)	147 (89.6)	228 (82.9)	490 (75.0)	< .0001
BB, HFrEF (n = 1226)	144 (45.9)	248 (74.3)	504 (87.2)	< .0001
MRA, LVEF < 35% (n = 801)	114 (51.4)	101 (47.4)	235 (64.2)	.0007
RASI + BB, HFrEF (n = 1226)	62 (19.8)	117 (35.0)	156 (27.0)	.0896
RASI + BB + MRA, HFrEF (n = 1226)	65 (20.7)	99 (29.6)	245 (42.4)	< .0001
Devices				
CRT-P	2 (0.4)	4 (0.6)	30 (2.3)	.0004
CRT-D	0 0 (0.0)	18 (2.7)	97 (7.4)	< .0001
ICD	16 (2.9)	40 (6.1)	184 (14.0)	< .0001

AF, atrial fibrillation; BB, beta-blockers; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy- pacing; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NA, not available; OAC, oral anticoagulants; RASI, renin-angiotensin system inhibitors
The data are expressed as No. (%).
[a] Patients receiving 5 or more non-HF drugs.
[b] LVEF ≥ 40% and previous MI/diabetes/hypertension.

Incidence and predictors of outcomes

During the 1-year follow-up, 308 patients died (12.2%) and 529 (21.0%) were hospitalized at least once: 216 (8.6%) for noncardiovascular causes, 360 (14.3%) for cardiovascular causes, and 210 (8.3%) for worsening HF. All-cause mortality did not change across the 3 periods (figure 2). The proportion hospitalized during 1 year, overall, for cardiovascular causes and for HF decompensations declined significantly (figure 2), while the percentage of those admitted for noncardiovascular causes was similar across cohorts.

Overall, 591 patients (23.5%) met the combined primary endpoint of all-cause mortality or cardiovascular hospitalization. On multivariable analysis, enrolment in 2006 to 2011 (hazard ratio [HR] 0.70; 95%CI, 0.55-0.90; $P = .004$) and 2012 to 2018 (HR, 0.61; 95%CI, 0.47-0.79; $P = .0002$) carried a lower risk of the primary outcome than recruitment in 1999 to 2005 after adjustment for acknowledged predictors of prognosis, considering LVEF as a continuous variable (figure 3, table 2 of the supplementary data). The results were similar when LVEF cutoff values for different HF phenotypes were instead included in the model (2006-2011 cohort HR, 0.69; 95%CI, 0.54-0.88; $P = .003$ and 2012-2018 cohort (HR, 0.60; 95%CI, 0.47-0.78; $P < .0001$).

HF-GDMT included in the same model as a composite variable was associated with a lower risk of mortality or cardiovascular hospitalization (HR, 0.76; 95%CI, 0.63-0.91; $P = .002$).

Figure 4 depicts direct adjusted survival curves for the primary endpoint in the 4 groups of polypharmacy intake: patients on non-HF polypharmacy alone had the worst prognosis (HR, 1.57 vs no polypharmacy, 95%CI, 1.18-2.09, $P = .002$).

DISCUSSION

Our nationwide registry data address an evidence gap by providing novel evidence about the evolving characteristics and outcomes over the last 2 decades of octogenarians, a burgeoning population segment in Western countries that carries the largest mortality and morbidity burden from HF (figure 5).

Our octogenarian cohort shares the peculiar clinical profile previously described in the elderly, although, in agreement with

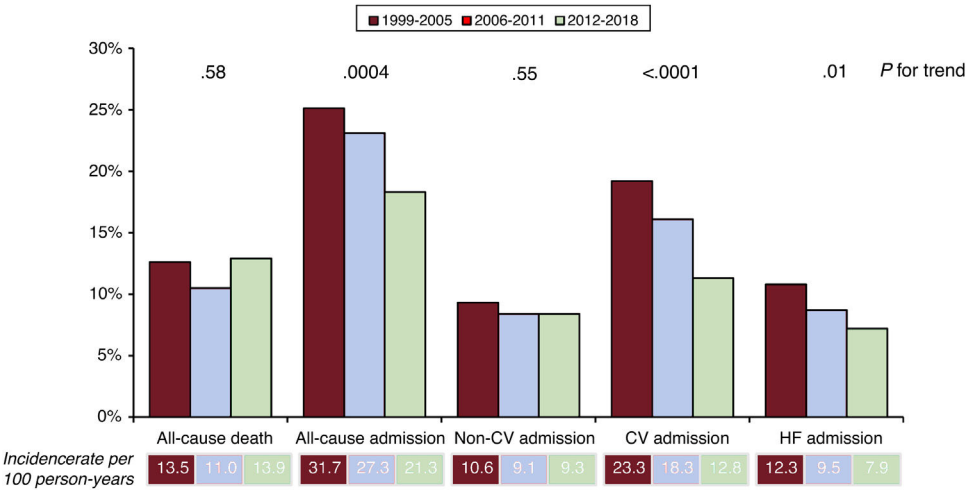

Figure 2. Cross-period comparison in the proportion of defunct and hospitalized patients. CV, cardiovascular; HF, heart failure.

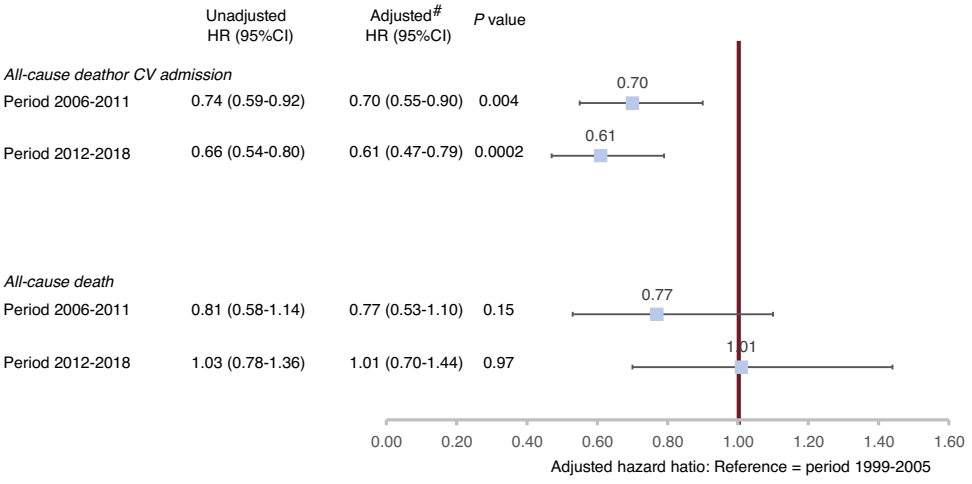

Figure 3. Association of enrolment period with outcome. Unadjusted and adjusted Cox models. * Adjusted by age, sex, heart failure (HF) etiology, duration of HF history, HF admission in the previous year, history of atrial fibrillation, pre-existing hypertension, diabetes, previous stroke/transient ischemic attack, NYHA class III-IV, body mass index, systolic blood pressure, heart rate bpm, LVEF%, furosemide, renin-angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, implanted cardioverter defibrillator/cardiac resynchronization therapy-defibrillator, and non-HF directed polypharmacy; covariates were selected based on clinical relevance and previous literature findings.

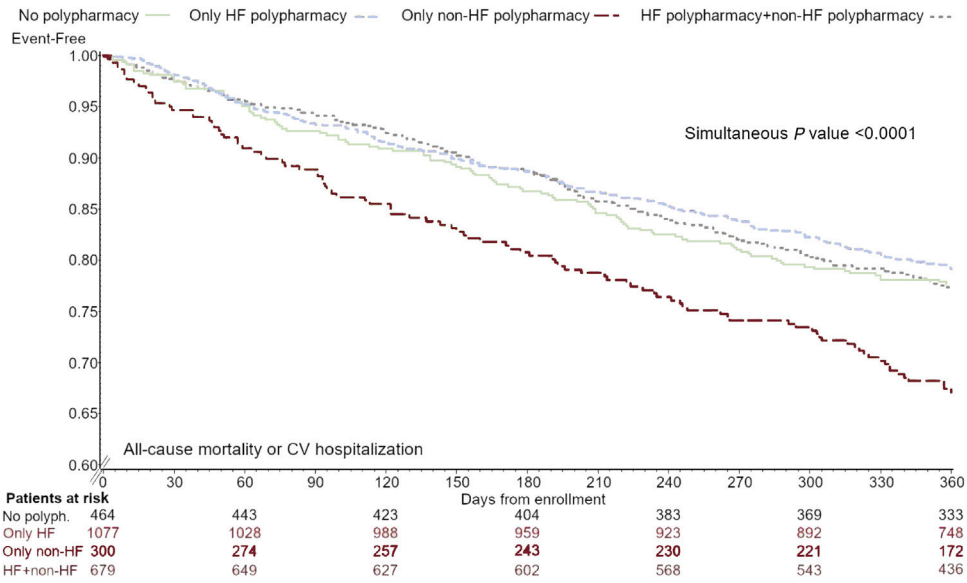

Figure 4. Kaplan-Meier curves for all-cause mortality or cardiovascular hospitalization according to drug treatment complexity, adjusted for age, ejection fraction, systolic blood pressure, study period, heart failure etiology, NYHA class, heart failure hospitalization in the last year, history of hypertension (covariates significant by backward selection in multivariable Cox regression). HF, heart failure.

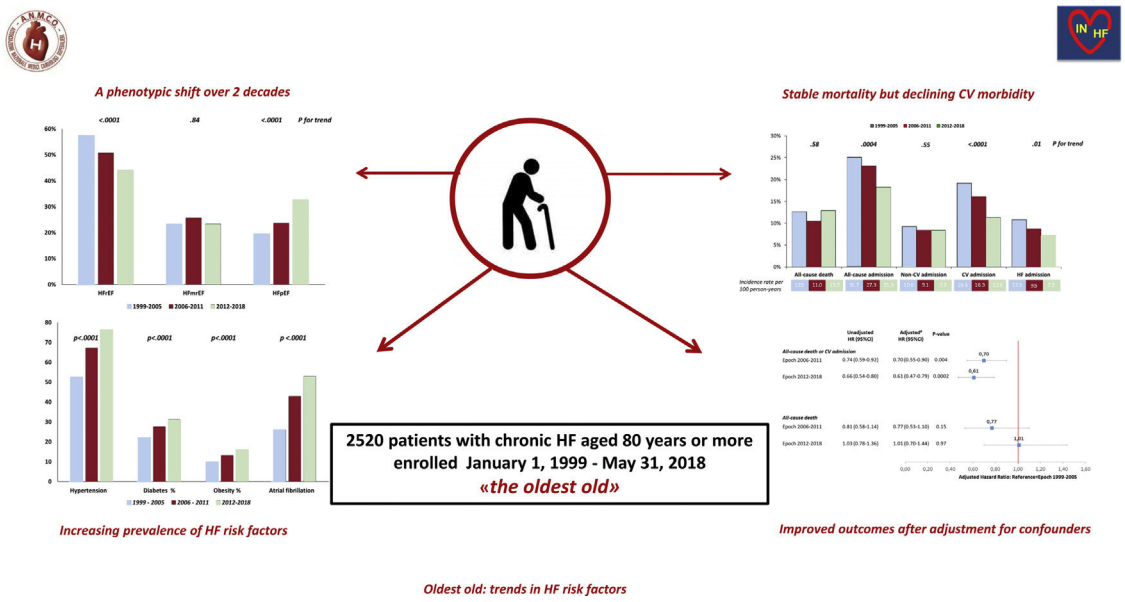

Figure 5. Central illustration. Temporal trends in clinical characteristics and treatment of octogenarians with chronic heart failure: changes over 2 decades in a nationwide cardiology registry.

enrolment and follow-up in the specialist cardiology setting, female prevalence (40%) was lower than in the general elderly population with HF.[5–9]

Our novel findings confirm in the oldest old the reported increase in HFpEF[10,11] as a companion effect of population aging, increasing prevalence of cardiometabolic risk factors,[16] and declining HFrEF incidence rates with improved management of myocardial infarction. Declining blood pressure and heart rate values, a likely expression of long-standing disease and more stringent implementation of drug therapy, suggest that octogenarians may have been more aggressively treated in recent periods, by greater BB and RASI uptake and boosted decongestion strategies.

Treatment changes

Patients older than 80 years have been underrepresented in clinical trials, leading to uncertainty about the efficacy of cornerstone therapies for HFrEF in this population.[24] Overzealous guideline implementation may not improve outcomes for very elderly patients, in whom competing comorbidity may more strongly affect prognosis.[25] Careful follow-up and therapeutic tailoring deriving from implementation of organizational changes at our multidisciplinary HF outpatient clinics, through nationwide networking and nurse-led education, deserve much of the credit, besides therapeutic interventions, for progress in care in such a delicate population.

In our octogenarians, 2 cornerstones HF therapies, MRA and BB, and anticoagulants in patients with atrial fibrillation were consistently implemented over time.

Treatment rates were superior both to those in the United Kingdom general HF population[3] and in the United States PINNACLE registry,[26] and aligned with the European Observational Research Program Heart Failure Long-Term Registry 2011 to 2016 data among participants with a median age of 66 years,[14] except for RASI. The CHECK investigators[8] also reported, among octogenarians with HFrEF seen at Dutch HF outpatient clinics in 2013 to 2016, higher prescription rates for BB than RASI. Aggressive decongestion, as suggested by more common high-dose[27] furosemide prescription in 2012 to 2018, and its attendant adverse effects of hypotension in the setting of impaired renal function, provide a putative justification for the decrease over time in RASI prescription and dosing: in our series, the odds of lower RASI prescription were associated with variables reflecting a mix of possible intolerance, drug interference, and uncertain indication.[28] When considering that 1 in 5 of our octogenarians did not receive RASI or BB, the evolving evidence of benefit and low adverse event rates from SGLT2 inhibitors in HF patients, irrespective of LVEF level,[29,30] paves the way[22] for novel drug prioritization strategies to improve the management of elderly HF patients.

Evolving prognosis

Very poor outcomes have consistently been reported in the elderly with HF[15] with no changes in mortality in multiple community-based cohort samples from 1990 to 2013.[15,26,31] One-year mortality in our most recent cohort (2012-2018) was 12.9%, a relatively small excess mortality compared with the 11.6% rate from our 2017 National Census[32] among participants aged 80 to 94 years. In the general population of this age group, HF may represent one of many comorbidities and geriatric syndromes influencing survival, while frail home-bound patients, those with logistic and transportation problems or other more severe and prioritized comorbidities, are less likely to attend outpatient clinics and receive specialist management.

Our registry data show a significant decline across 2 decades in the proportion of octogenarians with HF who were readmitted during the first year after enrolment. In agreement with previous findings in cardiology trial settings,[33] noncardiovascular causes accounted for over one third of readmissions, a proportion that did not change over time. The decrease in hospitalizations, which paralleled the uptake of oral anticoagulants, BB and MRA and, to a lesser extent, cardiac resynchronization therapy, was entirely linked to readmissions for cardiovascular causes and in particular for HF decompensation. Moreover, since the risk of stroke and HF hospitalization are similar in patients with atrial fibrillation and both HFrEF and HFpEF,[34] the implementation of anticoagulation might have substantially contributed to the declining proportion of cardiovascular hospitalizations across phenotypes in our series. Declining morbidity represents a pivotal achievement in a patient group that may be focused on the quality rather than the quantity of remaining life, particularly when severely symptomatic.[35]

The favorable trends in outcomes observed over the last 2 decades in our series will likely be deeply altered by the disproportionate pandemic impact on elderly HF patients.[36,37] Moreover, although telehealth intervention may be feasible during periods of restricted in-person access to outpatient facilities, without increases in subsequent hospital encounters or mortality,[38] oldest old patients, who face sensory and cognitive barriers to the use of technology, are likely to require specific provisions to access remote care.

Disentangling the impact of polypharmacy

Frailty and polypharmacy are both highly prevalent and linked to adverse outcomes in the elderly.[39,40] To account for the dual significance of polypharmacy, ie, a marker of greater GDMT prescription on the one hand and of clinical complexity on the other, in our HF outpatient clinic setting, we separately analyzed the 2 treatment components. The 2-fold increase in the proportion of participants on non-HF polypharmacy points to the expanding multimorbidity and clinical complexity of recruited patients across 2 decades. Patients with non-HF polypharmacy who did not receive HF-GDMT had the worst prognosis even after multivariate adjustment, suggesting that in our cohort this label may encompass unmeasured confounders linked to frailty. On the other hand, since polypharmacy may result in decreased therapeutic adherence and a higher risk of drug-related adverse events, accurate and complete medication reconciliation, and deprescribing of redundant medications, should represent a primary target during outpatient follow-up, to prevent avoidable hospitalizations in this age stratum.

Limitations

Our data derive from a long-term observational registry, which does not allow inferences on causation. Our findings cannot be extended to the general octogenarian population, since being on specialist follow-up might *per se* represent a selection bias. Changes in diagnostic methods over time might have impacted on LVEF values, together with a greater awareness of HFpEF as a clinical entity in cardiology practice and changes in hospital discharge coding accuracy. Laboratory data were consistently collected only in the 2 most recent cohorts. Natriuretic peptides, which seem to maintain their value as a marker of severity and outcomes in the elderly, were not available. We did not collect information on socioeconomic deprivation, quality of life, or cognitive, sensory, or motor impairment, which represent important dimensions with prognostic value in the assessment of geriatric populations.[41]

CONCLUSIONS

Over a 20-year period, the characteristics and outcomes of octogenarians enrolled in a nationwide HF registry have substantially changed, reflecting demographic variations, the evolution of cardiovascular risk factors, and improved implementation of BB, MRA, and electrical device therapy. The survival of octogenarians remained stable over time and on average close to that of the general population of the same age group, while the proportion admitted to hospital for cardiovascular causes declined. These data suggest that, despite increasing patient complexity, in the cardiology setting the burden of HF in the elderly is declining.

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AUTHORS' CONTRIBUTIONS

R. De Maria and L. Gonzini had full access to all of the data in the study and take responsibility for the integrity of the data and

the accuracy of the data analysis. Concept and design: R. De Maria, M. Iacoviello, M. Gori, and M. Marini. Acquisition, analysis, interpretation of data: M. Benvenuto, L. Cassaniti, A. Municinò, A. Navazio, E. Ammirati, G. Leonardi, N. Pagnoni, L. Montagna, M. Catalano, P. Midi, A.M. Floresta, and G. Pulignano. Drafting of the manuscript: R. De Maria, Mauro Gori, and L. Gonzini. Critical revision of the manuscript for important intellectual content: M. Benvenuto, L. Cassaniti, A. Municinò, A. Navazio, E. Ammirati, G. Leonardi, N. Pagnoni, L. Montagna, M. Catalano, P. Midi, A.M Floresta, and G. Pulignano. Statistical analysis: L. Gonzini. Supervision: M. Iacoviello.

CONFLICTS OF INTEREST

M. Benvenuto, L. Cassaniti, M. Catalano, R. De Maria, A.M. Floresta, L. Gonzini, M. Gori, M. Iacoviello, G. Leonardi, M. Marini, L. Montagna, A. Municinò, P. Midi, A. Navazio, N. Pagnoni, G. Pulignano have no conflicts of interest to disclose. E. Ammirati reports personal fees from KINIKSA PHARMACEUTICAL, during the conduct of the study.

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WHAT IS KNOWN ABOUT THE TOPIC?

Heart failure (HF) affects more than 10% of people older than 80 years, the fastest growing population segment in Europe. Data are scarce on the trend in risk factor prevalence, drug treatment and outcomes among octogenarians with chronic HF.

WHAT DOES THIS STUDY ADD?

Over 2 decades, the prevalence of cardiovascular risk factors and the preserved HF phenotype increased, while recommended therapies were steadily implemented. Although age at enrolment and polypharmacy rose, 1-year survival was stable, while the proportion of patients hospitalized for cardiovascular causes decreased. Octogenarians are increasingly managed in cardiology settings, with declining morbidity, despite increasing clinical complexity.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2022.03.002

REFERENCES

1. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol.* 2016;13:368–378.
2. Eurostat Statistics Explained. Population structure and ageing. 2021. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing. Accessed 23 Feb 2022.
3. Uijl A, Vaartjes I, Denaxas S, et al. Temporal trends in heart failure medication prescription in a population-based cohort study. *BMJ Open.* 2021;11:e043290.
4. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6:606–619.
5. Komajda M, Hanon O, Hochadel M, et al. Management of octogenarians hospitalized for heart failure in Euro Heart Failure Survey I. *Eur Heart J.* 2007;28:1310–1318.
6. Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J.* 2009;30:478–486.
7. Mogensen UM, Ersbøll M, Andersen M, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. *Eur J Heart Fail.* 2011;13:1216–1223.
8. Veenis JF, Brunner-La Rocca HP, Linssen GC, et al. CHECK-HF investigators. Age differences in contemporary treatment of patients with chronic heart failure and reduced ejection fraction. *Eur J Prev Cardiol.* 2019;26:1399–1407.
9. Lainščak M, Milinković I, Polovina M, et al. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2020;22:92–102.
10. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *JACC Heart Fail.* 2018;6:678–685.
11. Fröhlich H, Rosenfeld N, Täger T, et al. Epidemiology and long-term outcome in outpatients with chronic heart failure in Northwestern Europe. *Heart.* 2019;105:1252–1259.
12. Chamberlain AM, Boyd CM, Manemann SM, et al. Risk factors for heart failure in the community: differences by age and ejection fraction. *Am J Med.* 2020;133:e237–e248.
13. Tavazzi L, Senni M, Metra M, et al. IN-HF (Italian Network on Heart Failure) Outcome Investigators. Multicenter prospective observational study on acute and chronic heart failure: 1-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. *Circ Heart Fail.* 2013;6:473–481.
14. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail.* 2016;18:613–625.
15. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail.* 2019;21:1306–1325.
16. Senni M, De Maria R, Gregori D, et al. Temporal trends in survival and hospitalizations in outpatients with chronic systolic heart failure in 1995 and 1999. *J Cardiac Fail.* 2005;11:270–278.
17. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J.* 2001;22:1527–1560.
18. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). *Eur Heart J.* 2005;26:1115–1140.
19. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur J Heart Fail.* 2008;10:933–989.
20. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail.* 2012;14:803–869.
21. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J.* 2016;37:2129–2200.
22. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599–3726.
23. World Health Ortanization. Medication safety in polypharmacy: technical report. 2019. Available at: https://apps.who.int/iris/handle/10665/325454. Accessed 3 Mar 2022.
24. Vitale C, Fini M, Spoletini I, Lainscak M, Seferovic P, Rosano GM. Under-representation of elderly and women in clinical trials. *Int J Cardiol.* 2017;232:216–221.
25. Gorodeski EZ, Goyal P, Hummel SL, et al. Geriatric Cardiology Section Leadership Council, American College of Cardiology. Domain management approach to heart failure in the geriatric patient: present and future. *J Am Coll Cardiol.* 2018;71:1921–1936.
26. Maddox TM, Song Y, Allen J, et al. Trends in U.S. ambulatory cardiovascular care 2013 to 2017: JACC Review Topic of the week. *J Am Coll Cardiol.* 2020;75:93–112.
27. Wilcox CS, Testani JM, Pitt B. Pathophysiology of diuretic resistance and its implications for the management of chronic heart failure. *Hypertension.* 2020;76:1045–1054.
28. Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochr Database Syst Rev.* 2018;6:CD012721.
29. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet.* 2020;396:819–829.
30. Anker SD, Butler J, Filippatos G, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021;385:1451–1461.
31. Conrad N, Judge A, Canoy D, et al. Temporal trends and patterns in mortality after incident heart failure: a longitudinal analysis of 86000 individuals. *JAMA Cardiol.* 2019;4:1102–1111.
32. i.Stat, the complete data warehouse for experts. 2021. Available at: http://dati.istat.it/. Accessed 3 Mar 2022.

33. O'Connor CM, Miller AB, Blair JE, et al. Efficacy of Vasopressin Antagonism in heart Failure Outcome Study with Tolvaptan (EVEREST) investigators. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J.* 2010;159:841–849e1.
34. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol.* 2016;203:660–666.
35. Kraai IH, Vermeulen KM, Luttik ML, Hoekstra T, Jaarsma T, Hillege HL. Preferences of heart failure patients in daily clinical practice: quality of life or longevity? *Eur J Heart Fail.* 2013;15:1113–1121.
36. Sokolski M, Trenson S, Sokolska JM, et al. Heart failure in COVID-19: the multicentre, multinational PCHF-COVICAV registry. *ESC Heart Fail.* 2021;8:4955–4967.
37. Goyal P, Reshetnyak E, Khan S, et al. Clinical characteristics and outcomes of adults with a history of heart failure hospitalized for COVID-19. *Circ Heart Fail.* 2021;14:e008354.
38. Sammour Y, Spertus JA, Austin BA, et al. Outpatient management of heart failure during the COVID-19 pandemic after adoption of a telehealth model. *JACC Heart Fail.* 2021;9:916–924.
39. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc.* 2014;62:2261–2272.
40. Bottle A, Kim D, Hayhoe B, et al. Frailty and co-morbidity predict first hospitalisation after heart failure diagnosis in primary care: population-based observational study in England. *Age Ageing.* 2019;48:347–354.
41. Yang X, Lupón J, Vidán MT, et al. Impact of frailty on mortality and hospitalization in chronic heart failure: a systematic review and meta-analysis. *J Am Heart Assoc.* 2018;7:e008251.