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RESEARCH ARTICLE

Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata

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Aims In older patients, guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (<40%; HFrEF) is not contraindicated, but adherence to guidelines is limited. We investigated the implementation of GDMT in HFrEF across different age strata in a large nationwide cohort.

Methods and results Patients with HFrEF and HF duration ≥3 months registered in the Swedish HF Registry between 2000–2018 were analysed according to age. Multivariable logistic and multinomial regressions were fitted to investigate factors associated with underuse/underdosing. Of 27 430 patients, 31% were <70 years old, 34% 70–79 years old, and 35% ≥80 years old. Use of treatments progressively decreased with increasing age. Use of renin–angiotensin system/angiotensin receptor–neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists was 80%, 88% and 35% in age ≥80 years; 90%, 93% and 47% in age 70–79 years; and 95%, 95% and 54% in age <70 years, respectively. Among patients with an indication, use of implantable cardioverter defibrillator and cardiac resynchronization therapy (CRT) was 7% and 23% in age ≥ 80 years; 22% and 42% in age 70–79 years; and 29% and 50% in age <70 years, respectively. Older patients were less likely treated with target doses or combinations of HF medications. Except for CRT, after extensive adjustments, age was inversely associated with the likelihood of GDMT use and target dose achievement.

Conclusion In HFrEF, gaps persist in the use of medications and devices. In disagreement with current recommendations, older patients remain undertreated. Improving strategies and a more individualized approach for implementing use of GDMT in HFrEF are required, particularly in older patients.

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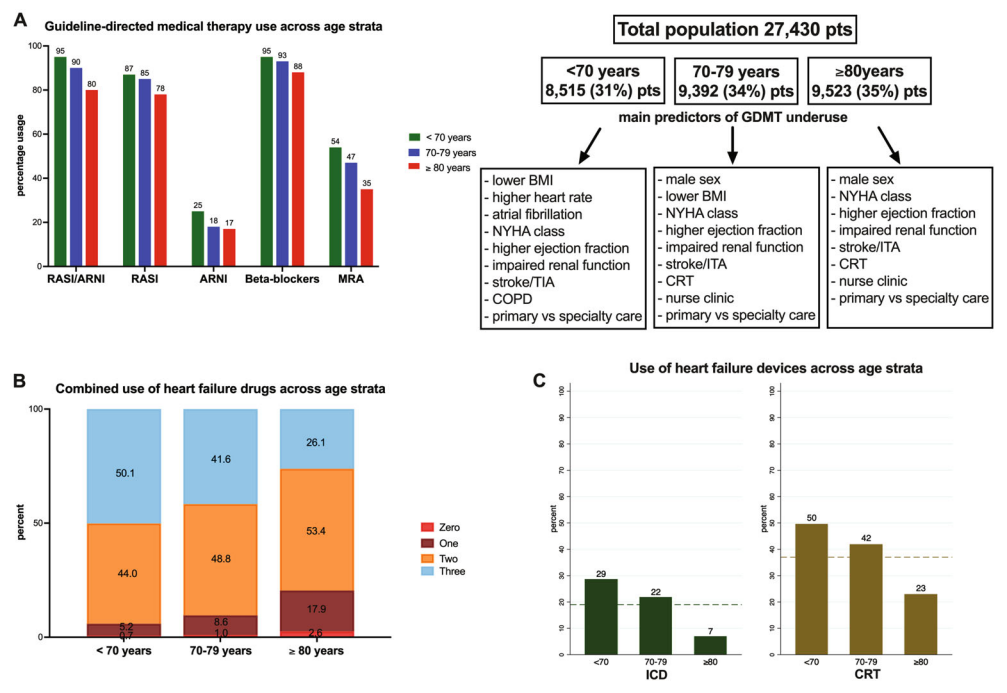
Graphical Abstract



Use of guideline-directed medical therapy (GDMT) across age strata in heart failure with reduced ejection. (*A*) Crude rate of guideline-directed medical therapy use in the overall cohort and across age strata. Angiotensin receptor–neprilysin inhibitor (ARNI) rates refer to patients enrolled from 2016 onward. (*B*) Combined use of heart failure drugs in the overall cohort and across age strata. (*C*) Crude use of heart failure devices across age strata. Dashed lines indicate the rates of implantation in the total population. BMI, body mass index; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Keywords Elderly • Heart failure with reduced ejection fraction • Guideline-directed medical therapy

Introduction

Randomized controlled trials (RCTs) enrol selected populations, and this may compromise generalizability and limit the implementation of their findings into clinical practice. Most RCTs in heart failure (HF) with reduced ejection fraction (HFrEF) do not explicitly exclude older patients, but these are often poorly represented, though HF is highly prevalent and incident in older populations.[1] Age *per se* is not a contraindication to guideline-directed medical therapy (GDMT),[2–4] but lower use of GDMT has frequently been observed in older patients.[5–10] Potential explanations might be perceived contraindications and reduced tolerance, patient preferences, or clinical inertia. Moreover, the limited evidence supporting the incremental prognostic effect of GDMT target dose (TD) achievement in older patients might lead clinicians to a more cautious approach to uptitration.[11–14] Finally, among older patients, the current GDMT implementation status in octogenarians is even more rarely investigated since this population was underrepresented in previous registry-based studies focused on the use of therapies.[6,7]

Therefore, the aim of this study was to provide a comprehensive overview on the current implementation status of HF evidence-based therapy and explore reasons for underuse/underdosing in a large and unselected national cohort of HFrEF patients across different age strata and within specific subgroups of interest.

Methods

Study population

Data from the Swedish HF Registry (SwedeHF) linked with the National Patient Registry and Statistics Sweden were analysed. Data sources are described in the online supplementary material.

Patients and treatments

For the current analysis, patients with HFrEF (ejection fraction [EF] <40%) and a HF duration ≥3 months (to allow for treatment

optimization) registered between 11 May 2000 and 31 December 2018 were considered. Patients who died during hospitalization or had re-used/changed personal identification numbers were excluded. If a patient was registered more than once, the last registration was selected as more representative of contemporary care.

Treatments analysed in the current study included renin–angiotensin system inhibitors (RASI, i.e. angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), angiotensin receptor–neprilysin inhibitors (ARNI; only from 2016), beta-blockers, mineralocorticoid receptor antagonists (MRA), implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT). For in-hospital patients, treatment at discharge was considered, i.e. when the patient was clinically stable.

Analyses on HF devices were conducted in patients who fulfilled the above-reported inclusion criteria and had a class I–IIa recommendation for ICD (New York Heart Association [NYHA] class II–III) or CRT (NYHA class ≥II, QRS duration ≥130 ms and left bundle branch block morphology or QRS duration ≥150 ms and non-left bundle branch block morphology) implantation according to the 2016 European Society of Cardiology (ESC) HF guidelines.[2]

The use of HF treatments and the proportion of TD received (as defined in the ESC HF guidelines – online supplementary *Table S1*) were assessed overall and according to three age categories: <70, 70–79 and ≥80 years.[2,4] Trends in use of HF treatments over time (starting from 2003 when SwedeHF was implemented nationally, with MRA doses available in the registry from 2015) and the combined use of HF treatments were also assessed. Use of treatments was also investigated according to caregiver location (in- vs. outpatient) for all treatments; estimated glomerular filtration rate (eGFR) for RASI-ARNI, ARNI and MRA (eGFR <30 vs. 30–60 vs. ≥60 ml/min/1.73 m^2); presence of dyskalaemia for RASI-ARNI, ARNI and MRA; heart rate and presence of atrial fibrillation for beta-blockers; EF for ICD (<30% vs. ≥30%); EF and presence of atrial fibrillation for CRT. Analyses were also performed in males and females separately. Variations in use of treatments across the different regions in Sweden were also assessed.

Statistical analysis

Continuous variables were reported as mean (± standard deviation) or median (interquartile range [IQR]) and compared by analysis of variance (ANOVA) or Mann–Whitney U test as appropriate, whereas categorical variables were reported as counts (percentages) and compared by chi-square test. Multivariable logistic and multinomial regression models were fitted to investigate patient characteristics independently associated with use/non-use of treatments and the achieved percentage of TD used for each of the study drugs (<50%, 50%–99%, and ≥100% of TD).

Risk-adjusted probabilities of HF treatment use over time and of ≥100% TD achievement were investigated in the overall population and within each age category by multivariable logistic regression analysis. Calendar year was included in the models to obtain the annual adjusted predicted probability of treatment use and TD achievement. Finally, to evaluate whether the probability of drug/device use or TD achievement changed over time, in the overall cohort and within the different age categories, logistic regression models were fitted including calendar year of registration as continuous covariate and drug/device use or TD achievement as dependent variables.

Variables included as covariates in the multivariable models are specified in *Table 1*.

In all multivariable models, missing data for patient characteristics were handled by chained equation multiple imputation (10 datasets generated, see online supplementary *Table S2* for percentage of missing data for each variable). More details are reported in online supplementary *Methods*.

A *p*-value of <0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed using Stata version 14.2 (Stata Corp., College Station, TX, USA) and GraphPad Prism version 8 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline characteristics

Study cohort selection is shown in online supplementary *Figure S1*. In 27 430 HFrEF patients who met the inclusion criteria for our analysis, mean age was 74 ± 12 years, with 31% <70 years old, 34% being 70–79 years old and 35% ≥80 years old. Overall, 27% were female, with the proportion of females increasing with aging (*Table 1*).

Older patients were more likely to live alone, to have lower education level and income, and to be registered as inpatients, but were less likely referred to specialty care or to a HF nurse-led clinic.

They were also more likely to have longer history of HF, higher NYHA class and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, but less likely to have EF <30%. Furthermore, older patients had a higher comorbidity burden (e.g. kidney disease, atrial fibrillation/atrial flutter, anaemia, hypertension, valve disease, ischaemic heart disease, history of stroke/transient ischaemic attack, cancer, musculoskeletal disease/connective tissue disease and dementia).

Use of heart failure treatments according to age

In the overall population, 88% received RASI or ARNI, 17% ARNI, 92% beta-blockers and 45% MRA (*Table 1* and online supplementary *Figure S2*).

Use of medical treatments steadily decreased with aging. Among patients ≥80 years old, 78%, 7%, 88% and 35%, received treatment with RASI, ARNI, beta-blockers and MRA, respectively. Conversely, use of diuretics and nitrates was higher in older vs. younger patients. TD of medications was achieved in less than 50% of the total study population (44% for RASI-ARNI, 36% for beta-blockers and 16% for MRA), with older vs. younger patients less likely to be treated with TD (*Figure 1* and online supplementary *Figure S2*) or to receive combinations of HF treatments, i.e. 26% vs. 50% receiving three treatments in age ≥ 80 vs. <70 years (*Graphical Abstract* and online supplementary *Figure S2*).

In patients with an indication for a HF device (ICD = 19 444 patients; CRT = 8444 patients), 19% had an ICD and 37% a CRT (online supplementary *Figure S2*). The crude use of ICD and CRT was nearly four-fold and two-fold lower in patients ≥80 vs. <70 years old, whereas the use of HF devices in patients 70–79 years old was more similar to that in patients <70 years old (*Graphical Abstract*). Lower use of GDMT in older vs. younger patients was consistent across the different regions in Sweden (online suppementary *Figures S3* and *S4*).

Table 1 Main characteristics of the study population according to age category

	Total	Age category			*p*-value
		<70 years	70–79 years	≥80 years	
Patients, *n* (%)	27 430	8515 (31)	9392 (34)	9523 (35)	
Demographics					
Age, years[c], mean (SD)	74 (12)	60 (9)	75 (3)	85 (4)	<0.001
Female sex[c], *n* (%)	7484 (27)	1836 (22)	2428 (26)	3220 (34)	<0.001
Caregiver at SwedeHF registration[c], *n* (%)					<0.001
Inpatient	10 079 (37)	2188 (26)	3038 (32)	4853 (51)	
Outpatient	17 351 (63)	6327 (74)	6354 (68)	4670 (49)	
Follow-up referral to outpatient HF nurse-led clinic[c], *n* (%)					<0.001
No	12 155 (47)	3127 (38)	3876 (44)	5152 (58)	
Yes	13 679 (53)	4990 (62)	4982 (56)	3707 (42)	
Follow-up referral specialty[c], *n* (%)					<0.001
Hospital	17 788 (68)	7035 (85)	6520 (73)	4233 (47)	
Primary care	7519 (29)	998 (13)	2156 (24)	4365 (49)	
Other	828 (3)	194 (2)	281 (3)	353 (4)	
Socio-economic, *n* (%)					
Family type[c]					<0.001
Cohabitating	14 463 (53)	4538 (54)	5378 (57)	4547 (48)	
Living alone	12 931 (47)	3951 (46)	4008 (43)	4972 (52)	
Education[c]					<0.001
Compulsory	12 155 (45)	2775 (33)	4233 (46)	5147 (55)	
Secondary	10 508 (39)	4021 (48)	3498 (38)	2989 (32)	
University	4197 (16)	1573 (19)	1465 (16)	1159 (13)	
Income[c]					<0.001
Low	9589 (35)	2606 (31)	3313 (35)	3670 (39)	
Medium	10 537 (39)	2356 (28)	4026 (43)	4155 (44)	
High	7268 (26)	3527 (41)	2047 (22)	1694 (17)	
Children[c]	22 792 (83)	6434 (76)	8026 (85)	8332 (88)	<0.001
Clinical					
HF duration <6 months[c], *n* (%)	5467 (20)	2052 (24)	1771 (19)	1644 (17)	<0.001
BMI, kg/m^2[c], *n* (%)					<0.001
<22.5		627 (13)	901 (17)	1566 (29)	
22.5–30		2443 (52)	3095 (59)	3177 (58)	
>30		1641 (35)	1269 (24)	698 (13)	
NYHA class III–IV[c], *n* (%)	10 798 (50)	2737 (39)	3862 (51)	4199 (61)	<0.001
Blood pressure, mmHg, mean (SD)					
Systolic	122 (20)	121 (20)	122 (20)	123 (20)	<0.001
Diastolic	71 (12)	73 (12)	71 (11)	70 (11)	<0.001
Mean[c,d]	88 (13)	89 (13)	88 (13)	88 (13)	<0.001
Heart rate, bpm[c], mean (SD)	73 (15)	72 (15)	73 (15)	74 (15)	<0.001
LVEF <30%[c], *n* (%)	13 410 (49)	4394 (52)	4627 (49)	4389 (46)	<0.001
QRS duration, ms, mean (SD)	125 (32)	120 (30)	126 (32)	128 (32)	<0.001
Left bundle branch block, *n* (%)	5880 (28)	1478 (22)	2048 (29)	2354 (32)	<0.001
Laboratory					
Haemoglobin, g/L, mean (SD)	132 (17)	137 (17)	132 (17)	127 (16)	<0.001
Potassium, mEq/L, median (Q1–Q3)	4.3 (4.0–4.6)	4.3 (4.0–4.6)	4.3 (4.0–4.6)	4.2 (3.9–4.5)	<0.001
Dyskalaemia[c], *n* (%)					<0.001
Hypokalaemia	780 (4)	184 (3)	252 (3)	344 (5)	
Normakalaemia	19 647 (91)	6289 (93)	6829 (92)	6529 (90)	
Hyperkalaemia	1032 (5)	296 (4)	385 (5)	351 (5)	
eGFR, ml/min/1.73 m^2[a,c], *n* (%)					<0.001
<30	3238 (12)	428 (5)	954 (10)	1856 (20)	
30–60	12 191 (45)	2054 (25)	4583 (50)	5554 (59)	
≥60	11 486 (43)	5850 (70)	3653 (40)	1983 (21)	
NT-proBNP, pg/ml[c], median (Q1–Q3)	2669 (1040–6544)	1305 (509–3420)	2624 (1165–6000)	4820 (2311–10 681)	<0.001

Table 1 (Continued)

	Total	Age category			*p*-value
		<70 years	70–79 years	≥80 years	
Comorbidities, *n* (%)					
Atrial fibrillation/flutter[c]	16 343 (60)	3807 (45)	5925 (63)	6611 (69)	<0.001
Smoking[c]					<0.001
Current	2553 (12)	1480 (21)	785 (11)	288 (4)	
Former	10 169 (47)	3212 (47)	3852 (51)	3105 (43)	
Never	8845 (41)	2211 (32)	2846 (38)	3788 (53)	
Anaemia[b,c]	9625 (37)	2063 (26)	3278 (38)	4284 (47)	<0.001
Diabetes[c]	8922 (32)	2807 (33)	3453 (37)	2662 (28)	<0.001
Hypertension[c]	17 480 (64)	4694 (55)	6238 (66)	6548 (69)	<0.001
Valve disease[c]	8346 (31)	1906 (23)	2866 (31)	3574 (38)	<0.001
Ischaemic heart disease[c]	18 351 (67)	4610 (54)	6673 (71)	7068 (74)	<0.001
Previous revascularization	11 493 (42)	3194 (37)	4505 (48)	3794 (40)	<0.001
Peripheral artery disease[c]	3158 (11)	729 (9)	1318 (14)	1111 (12)	<0.001
Stroke or transient ischaemic attack[c]	5802 (21)	1281 (15)	2072 (22)	2449 (26)	<0.001
COPD[c,d]	4289 (16)	1161 (14)	1705 (18)	1423 (15)	<0.001
Liver disease[c]	759 (3)	450 (5)	190 (2)	119 (1)	<0.001
Cancer history in last 3 years[c]	4025 (15)	692 (8)	1505 (16)	1828 (19)	<0.001
Muscoloskeletal/connective tissue disease in last 3 years[c]	8844 (32)	2293 (27)	3170 (34)	3381 (35)	<0.001
Dementia[c]	538 (2)	31 (0.4)	206 (2)	301 (3)	<0.001
Depression[c]	1163 (4)	474 (6)	362 (4)	327 (3)	<0.001
Therapy and devices, *n* (%)					
RASI-ARNI[c]	23 904 (88)	7995 (95)	8384 (90)	7525 (80)	<0.001
RASI	22 732 (83)	7375 (87)	7917 (85)	7440 (78)	<0.001
ARNI	1349 (17)	669 (25)	524 (17)	156 (7)	<0.001
RASI target dose					<0.001
<50%	6490 (29)	1405 (19)	2165 (27)	2920 (39%)	
50%–99%	6157 (27)	1741 (24)	2129 (27)	2287 (31%)	
≥100	10 056 (44)	4222 (57)	3612 (46)	2222 (30%)	
ARNI target dose					0.005
<50%	311 (23)	140 (21)	120 (23)	51 (33)	
50%–99%	472 (35)	223 (33)	198 (38)	51 (33)	
≥100	566 (42)	306 (46)	206 (39)	54 (34)	
Beta-blocker[c]	25 094 (92)	8049 (95)	8734 (93)	8311 (88)	<0.001
Beta-blocker target dose					<0.001
<50%	7237 (29)	1692 (21)	2332 (27)	3213 (40)	
50%–99%	8490 (35)	2608 (33)	3038 (35)	2844 (35)	
≥100%	8901 (36)	3645 (46)	3209 (38)	2047 (25)	
MRA[c,d]	12 360 (45)	4572 (54)	4433 (47)	3355 (35)	<0.001
MRA target dose					<0.001
<50%	864 (13)	239 (9)	319 (13)	306 (19)	
50%–99%	4769 (71)	1820 (70)	1802 (73)	1147 (72)	
≥100%	1052 (16)	550 (21)	356 (14)	146 (9)	
Diuretics[c]	22 593 (83)	6238 (74)	7751 (83)	8604 (91)	<0.001
Digoxin[c]	4281 (16)	1260 (15)	1537 (16)	1484 (16)	0.015
Antiplatelet therapy[c]	11 840 (43)	3497 (41)	3935 (42)	4408 (47)	<0.001
Anticoagulant therapy[c]	13 445 (49)	3836 (45)	5121 (55)	4488 (47)	<0.001
Statin[c]	14 569 (53)	4653 (55)	5738 (61)	4178 (44)	<0.001
Nitrates[c]	4708 (17)	781 (9)	1536 (16)	2391 (25)	<0.001
ICD[c,d]	3755 (19)	1803 (29)	1529 (22)	423 (7)	<0.001
CRT[c,d]	3141 (37)	1140 (50)	1309 (42)	692 (23)	<0.001

ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASI, renin–angiotensin system inhibitor; SD, standard deviation.

[a]Calculated by the Chronic Kidney Disease Epidemiology Collaboration formula.

[b]Anaemia defined as haemoglobin <120 g/L in females and <130 g/L in males.

[c]Variables included in the multiple imputation models and as covariates in the multivariable models.

[d]Among patients with indication according to current guidelines (see Methods).

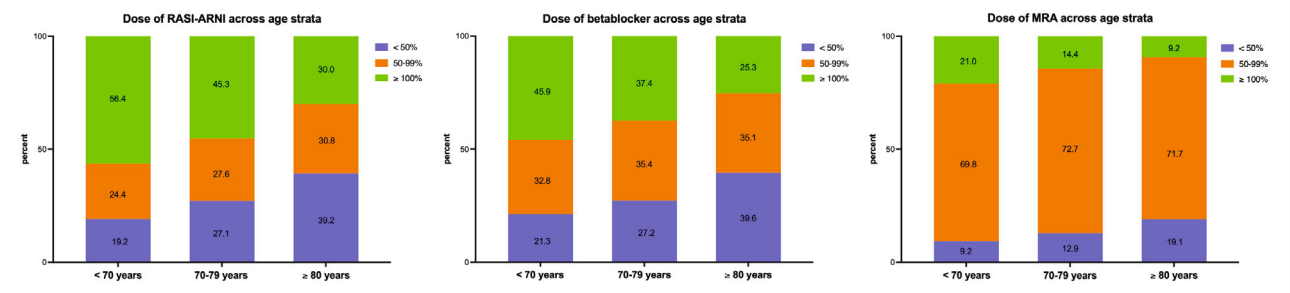


Figure 1 Target dose achievement of guideline-directed medical therapies in the overall cohort and across age strata. Doses of mineralocorticoid receptor antagonists (MRA) were available from 2015. ARNI, angiotensin receptor–neprilysin inhibitor; RASI, renin–angiotensin system inhibitor.

Differences in use of treatments across age categories are unadjusted and might be explained by age-related differences in patient characteristics. However, after comprehensive adjustments, there was still a significant independent association between older age and non-use and lower use of TD of antineurohormonal drugs, and lower use of ICD but not of CRT (online supplementary *Figure S5*).

Age-related differences in the use of heart failure treatments in specific subgroups

Use of treatments was overall lower in older vs. younger patients in all the explored subgroups. More specifically, a lower use of RASI-ARNI, ARNI and MRA was observed in patients with vs. without dyskalaemia, with more impaired renal function, and inpatients vs. outpatients. Beta-blocker use was slightly lower with heart rate >70 vs. ≤70 bpm and in inpatients vs. outpatients. In ≥80-year-old patients, the use of beta-blockers was slightly higher in those with vs. without concomitant atrial fibrillation (*Table 2*).

In the <70-year stratum, females were less likely treated with RASI-ARNI and beta-blockers compared with males, and use of ARNI was lower in females vs. males aged ≥70 years. Use of devices was consistently lower in females across all age categories. After extensive adjustments, older age was independently associated with non-use of RASI-ARNI and beta-blockers in males but not in females, whereas for MRA this association was consistent regardless of sex (online supplementary *Table S3*). The independent association of increasing age with less TD achievement and less ICD use, as well as the lack of association between age and CRT use, were consistent in males and females (online supplementary *Table S3*).

Independent predictors of use of heart failure treatments according to age

Regardless of age, better renal function was independently associated with use/TD achievement of RASI-ARNI and MRA. Referral to specialty care and nurse-led HF clinic was independently associated with higher use of HF drugs, whereas higher comorbidity burden with lower use/uptitration of HF drugs and lower use of ICD (*Table 3*, and online supplementary *Tables S3–S8*, *Figures S6* and *S7*).

In the age stratum ≥80 years, female sex was independently associated with higher use of RASI-ARNI and MRA, higher use and higher TD achievement of beta-blockers, and lower use of ICD, whereas in patients <70 years old female sex was independently associated with less TD achievement of RASI-ARNI and beta-blockers, but not with underuse of HF drugs or devices.

Atrial fibrillation was independently associated with lower use of RASI-ARNI and MRA in <70-year-old patients, lower use/dosing of RASI-ARNI in those aged ≥80 years, higher dose of beta-blockers in all age strata, higher use of CRT in those aged 70–79 and ≥80 years. CRT was independently associated with increased use of MRA in 70–79-year-old patients and of RASI-ARNI and beta-blockers in those aged ≥80 years.

Temporal trends in use of heart failure treatments across age categories

Crude rates of HF treatment use over time are reported in online supplementary *Figure S8* and *Table S9*. Use of RASI-ARNI was constantly lower in patients ≥80 years old, and the observed reduction in use of RASI between 2017 and 2018 in patients <80 years old was paralleled by an increase in use of ARNI . Similarly, use of beta-blockers and MRA was lower in the ≥80-year-old age category, but temporal trends in their use were similar to those in the overall population.

The adjusted predicted probabilities of using HF treatments over time are shown in *Figure 2* and online supplementary *Table S10*. Use of RASI-ARNI tended to decrease regardless of age, but more in the ≥80-year-old category compared with younger patients, whereas beta-blocker use increased in the age category ≥70 vs. <70 years. Use of MRA increased over time in the age category <80 years, but with only a non-statistically significant trend in patients ≥80 years old (*Figure 2*).

Temporal trends for crude use of TD of antineurohormonal drugs across the age classes were consistent with the data from the overall population, except for a slight decrease in TD use of MRA in patients ≥80 years old (online supplementary *Table S9*

Table 2 Use of guideline-directed medical therapy across age categories

	Total (*n* = 27 430)	Age category		
		<70 years (*n* = 8515)	70–79 years (*n* = 9392)	≥80 years (*n* = 9523)
RASI-ARNI, %				
Sex				
Male (*n* = 19 946)	88	95	90	80
Female (*n* = 7484)	87	93	91	80
p-value	<0.001	0.005	0.434	0.556
Dyskalaemia				
Hypokalaemia (*n* = 780)	72	86	75	63
Normakalaemia (*n* = 19 647)	89	95	91	82
Hyperkalaemia (*n* = 1032)	88	93	89	83
p-value	<0.001	<0.001	<0.001	<0.001
eGFR, ml/min/1.73 m^2				
<30 (*n* = 3238)	65	75	66	62
30–60 (*n* = 12 191)	87	92	91	83
≥60 (*n* = 11 486)	95	97	95	88
p-value	<0.001	<0.001	<0.001	<0.001
Caregiver at SwedeHF registration				
Inpatients (*n* = 10 079)	79	90	82	72
Outpatients (*n* = 17 351)	93	96	94	88
p-value	<0.001	<0.001	<0.001	<0.001
ARNI, %				
Sex				
Male (*n* = 19 946)	18	25	20	7
Female (*n* = 7484)	12	24	11	5
p-value	<0.001	0.612	<0.001	0.036
Dyskalaemia				
Hypokalaemia (*n* = 780)	9	18	9	3
Normakalaemia (*n* = 19 647)	17	25	18	7
Hyperkalaemia (*n* = 1032)	20	28	21	11
p-value	0.005	0.351	0.081	0.049
eGFR, ml/min/1.73 m^2				
<30 (*n* = 3238)	7	13	9	3
30–60 (*n* = 12 191)	15	27	19	7
≥60 (*n* = 11 486)	21	26	18	9
p-value	<0.001	0.017	0.001	0.002
Caregiver at SwedeHF registration				
Inpatients (*n* = 10 079)	4	12	3	1
Outpatients (*n* = 17 351)	19	26	20	9
p-value	<0.001	<0.001	<0.001	<0.001
Beta-blockers, %				
Sex				
Male (*n* = 19 946)	92	95	93	87
Female (*n* = 7484)	91	93	94	89
p-value	0.167	<0.001	0.363	0.020
Heart rate				
>70 bpm (*n* = 12 819)	91	94	93	87
≤70 bpm (*n* = 13 285)	93	96	94	88
p-value	<0.001	<0.001	0.093	0.082
Atrial fibrillation				
Yes (*n* = 16 343)	92	95	93	88
No (*n* = 11 087)	92	95	93	86
p-value	0.402	0.403	0.696	0.005
Caregiver at SwedeHF registration				
Inpatients (*n* = 10 079)	88	93	91	86
Outpatients (*n* = 17 351)	93	95	94	90
p-value	<0.001	<0.001	<0.001	<0.001

Table 2 (Continued)

	Total (n = 27 430)	Age category		
		<70 years (n = 8515)	70–79 years (n = 9392)	≥80 years (n = 9523)
MRA, %				
Sex				
Male (n = 19 946)	46	54	48	35
Female (n = 7484)	43	53	47	36
p-value	<0.001	0.136	0.350	0.849
Dyskalaemia				
Hypokalaemia (n = 780)	39	47	39	35
Normakalaemia (n = 19 647)	46	55	48	35
Hyperkalaemia (n = 1032)	51	57	52	44
p-value	<0.001	0.088	0.005	0.003
eGFR, ml/min/1.73 m^2				
<30 (n = 3238)	26	27	29	24
30–60 (n = 12 191)	44	54	48	37
≥60 (n = 11 486)	51	56	51	40
p-value	<0.001	<0.001	<0.001	<0.001
Caregiver at SwedeHF registration				
Inpatients (n = 10 079)	40	52	43	33
Outpatients (n = 17 351)	48	55	49	38
p-value	<0.001	0.026	<0.001	<0.001
ICD, %				
Sex				
Male (n = 19 946)	22	30	25	8
Female (n = 7484)	12	23	14	4
p-value	<0.001	<0.001	<0.001	<0.001
LVEF				
<30% (n = 13 410)	12	14	21	7
≥30% (n = 14 020)	16	18	13	4
p-value	<0.001	<0.001	<0.001	<0.001
Caregiver at SwedeHF registration				
Inpatients (n = 10 079)	20	38	24	6
Outpatients (n = 17 351)	19	26	21	7
p-value	0.082	<0.001	0.003	0.185
CRT, %				
Sex				
Male (n = 19 946)	40	52	44	26
Female (n = 7484)	29	41	36	15
p-value	<0.001	<0.001	<0.001	<0.001
LVEF				
<30% (n = 13 410)	41	53	44	25
≥30% (n = 14 020)	32	44	39	20
p-value	<0.001	<0.001	0.002	<0.001
Atrial fibrillation				
Yes (n = 16 343)	40	56	46	26
No (n = 11 087)	33	44	35	17
p-value	<0.001	<0.001	<0.001	<0.001
Caregiver at SwedeHF registration				
Inpatients (n = 10 079)	33	57	39	18
Outpatients (n = 17 351)	39	47	43	27
p-value	<0.001	<0.001	0.057	<0.001

ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RASI, renin–angiotensin system inhibitor.

Table 3 Factors associated with the use of guideline-directed heart failure medical therapy in the overall population

Variables	RASI/ARNI		Beta-blockers		MRA	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Male sex	0.79 (0.72–0.88)	<0.001	0.82 (0.73–0.91)	<0.001	0.92 (0.86–0.98)	0.007
Caregiver (outpatient vs. inpatient)	1.72 (1.56–1.89)	<0.001	1.18 (1.05–1.33)	0.004	0.91 (0.86–0.98)	0.007
Follow-up location						
Primary care vs. hospital	0.80 (0.72–0.88)	<0.001	0.77 (0.68–0.86)	<0.001	0.78 (0.73–0.83)	<0.001
Other vs. hospital	0.76 (0.62–0.94)	0.011	0.76 (0.60–0.97)	0.028	0.68 (0.58–0.79)	<0.001
Referral to HF nurse-led clinic	1.28 (1.15–1.42)	<0.001	1.12 (1.00–1.26)	0.052	0.98 (0.93–1.05)	0.627
HF duration (≥6 vs. <6 months)	0.88 (0.78–0.98)	0.024	0.81 (0.72–0.91)	0.001	1.23 (1.16–1.32)	<0.001
NYHA class (III–IV vs. I–II)	0.75 (0.68–0.84)	<0.001	0.8 8(0.79–0.99)	0.039	1.17 (1.10–1.24)	<0.001
BMI, kg/m^2						
22.5–30 vs. <22.5	1.38 (1.18–1.62)	<0.001	1.16 (1.00–1.34)	0.055	0.99 (0.90–1.08)	0.826
>30 vs. <22.5	1.40 (1.12–1.74)	0.004	1.25 (1.03–1.53)	0.027	1.20 (1.04–1.39)	0.013
MAP (≥90 vs. <90 mmHg)	1.03 (0.94–1.13)	0.489	1.06 (0.97–1.17)	0.201	0.76 (0.72–0.80)	<0.001
Heart rate (≥70 vs. <70 bpm)	0.76 (0.70–0.83)	<0.001	0.89 (0.81–0.98)	0.019	0.93 (0.89–0.98)	0.007
LVEF <30%	1.29 (1.18–1.40)	<0.001	1.07 (0.98–1.18)	0.147	1.20 (1.14–1.27)	<0.001
NT-proBNP (≥ median vs. <median)	0.65 (0.55–0.89)	<0.001	1.35 (1.09–1.67)	0.007	0.99 (0.90–1.10)	0.891
eGFR, mL/min/1.73 m^2						
30–60 vs. <30	2.92 (2.63–3.24)	<0.001	0.89 (0.77–1.02)	0.097	2.16 (1.96–2.37)	<0.001
>60 vs. <30	5.17 (4.50–5.94)	<0.001	0.84 (0.71–0.99)	0.047	2.77 (2.50–3.07)	<0.001
Dyskalaemia						
Normo vs. hypo	2.10 (1.69–2.60)	<0.001	0.90 (0.64–1.27)	0.542	1.10 (0.92–1.31)	0.200
Hyper vs. hypo	2.89 (2.22–3.75)	<0.001	0.92 (0.62–1.36)	0.677	1.54 (1.27–1.88)	<0.001
Ischaemic heart disease	0.80 (0.72–0.89)	<0.001	0.95 (0.85–1.06)	0.382	0.96 (0.90–1.02)	0.180
Hypertension	1.09 (1.00–1.20)	0.057	1.20 (1.09–1.33)	<0.001	1.12 (1.06–1.19)	<0.001
Diabetes mellitus	0.92 (0.83–1.01)	0.065	1.09 (0.98–1.21)	0.104	1.01 (0.95–1.08)	0.686
COPD	0.90 (0.80–1.01)	0.070	0.92 (0.81–1.05)	0.221	0.95 (0.88–1.02)	0.155
Anaemia	0.94 (0.86–1.02)	0.152	0.87 (0.79–0.96)	0.007	0.89 (0.84–0.94)	<0.001
Atrial fibrillation/flutter	0.82 (0.74–0.91)	<0.001	1.00 (0.90–1.13)	0.934	0.96 (0.90–1.03)	0.281
Peripheral artery disease	0.85 (0.75–0.96)	0.008	0.87 (0.76–0.99)	0.048	0.94 (0.87–1.02)	0.144
Stroke or transient ischaemic attack	0.83 (0.76–0.91)	<0.001	0.87 (0.78–0.96)	0.008	0.87 (0.82–0.93)	<0.001
Valvular disease	0.70 (0.64–0.76)	<0.001	0.83 (0.76–0.92)	<0.001	1.14 (1.08–1.21)	<0.001
Liver disease	0.71 (0.57–0.90)	0.004	1.01 (0.77–1.33)	0.949	1.12 (0.96–1.31)	0.140
Cancer history	0.87 (0.79–0.97)	0.013	0.90 (0.80–1.01)	0.076	0.94 (0.84–1.01)	0.117
Muscoloskeletal/connective tissue disease in last 3 years	0.86 (0.79–0.93)	<0.001	0.83 (0.75–0.91)	<0.001	0.90 (0.85–0.95)	<0.001
Dementia	0.86 (0.67–1.08)	0.182	1.21 (0.91–1.62)	0.195	0.81 (0.67–0.98)	0.034
Depression	1.03 (0.84–1.26)	0.775	0.73 (0.60–0.88)	0.002	1.04 (0.92–1.19)	0.482
Smoking						
Previous vs. current	0.86 (0.70–1.04)	0.116	0.78 (0.65–0.93)	0.007	1.12 (1.03–1.23)	0.012
No vs. current	0.82 (0.68–1.00)	0.052	0.72 (0.60–0.87)	0.001	1.11 (1.01–1.23)	0.028
Living alone vs. married/cohabitating	0.95 (0.87–1.04)	0.290	0.96 (0.87–1.06)	0.433	0.97 (0.92–1.03)	0.336
Education						
Secondary vs. compulsory	1.09 (0.99–1.20)	0.064	1.01 (0.91–1.11)	0.963	0.98 (0.92–1.04)	0.457
University vs. compulsory	1.20 (1.04–1.37)	0.011	0.98 (0.84–1.13)	0.756	0.98 (0.91–1.06)	0.681
Income						
Medium vs. low	1.02 (0.92–1.12)	0.756	1.00 (0.90–1.11)	0.963	1.06 (0.99–1.12)	0.067
High vs. low	0.99 (0.88–1.12)	0.952	1.13 (0.99–1.29)	0.078	1.13 (1.05–1.21)	0.001
Children	1.00 (0.89–1.13)	0.995	0.89 (0.78–1.01)	0.068	1.04 (0.97–1.12)	0.274
Diuretics	1.16 (1.00–1.34)	0.046	1.18 (1.03–1.35)	0.018	1.48 (1.37–1.59)	<0.001
Digoxin	1.13 (1.00–1.28)	0.045	1.12 (0.98–1.28)	0.094	1.28 (1.19–1.38)	<0.001
Nitrates	1.02 (0.92–1.13)	0.743	1.22 (1.08–1.38)	0.002	0.98 (0.92–1.06)	0.665
Anticoagulants	1.68 (1.49–1.89)	<0.001	1.60 (1.41–1.83)	<0.001	1.11 (1.03–1.20)	0.007
Antiplatelets	1.19 (1.07–1.33)	0.002	1.30 (1.15–1.47)	<0.001	0.95 (0.88–1.02)	0.123
Statins	1.58 (1.44–1.73)	<0.001	1.46 (1.32–1.62)	<0.001	1.07 (1.01–1.13)	0.026
RASI	–	–	1.99 (1.77–2.24)	<0.001	1.07 (0.98–1.17)	0.132
Beta-blockers	2.09 (1.86–2.35)	<0.001	2.00 (1.78–2.25)	<0.001	1.09 (0.99–1.20)	0.065
MRA	1.09 (0.99–1.19)	0.065	1.11 (1.01–1.22)	0.027	–	–
CRT	1.00 (0.85–1.18)	0.995	1.29 (1.05–1.58)	0.015	1.15 (1.05–1.26)	0.003
ICD	1.15 (0.97–1.36)	0.117	1.86 (1.50–2.32)	<0.001	1.49 (1.36–1.63)	<0.001

ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASI, renin–angiotensin system inhibitor.

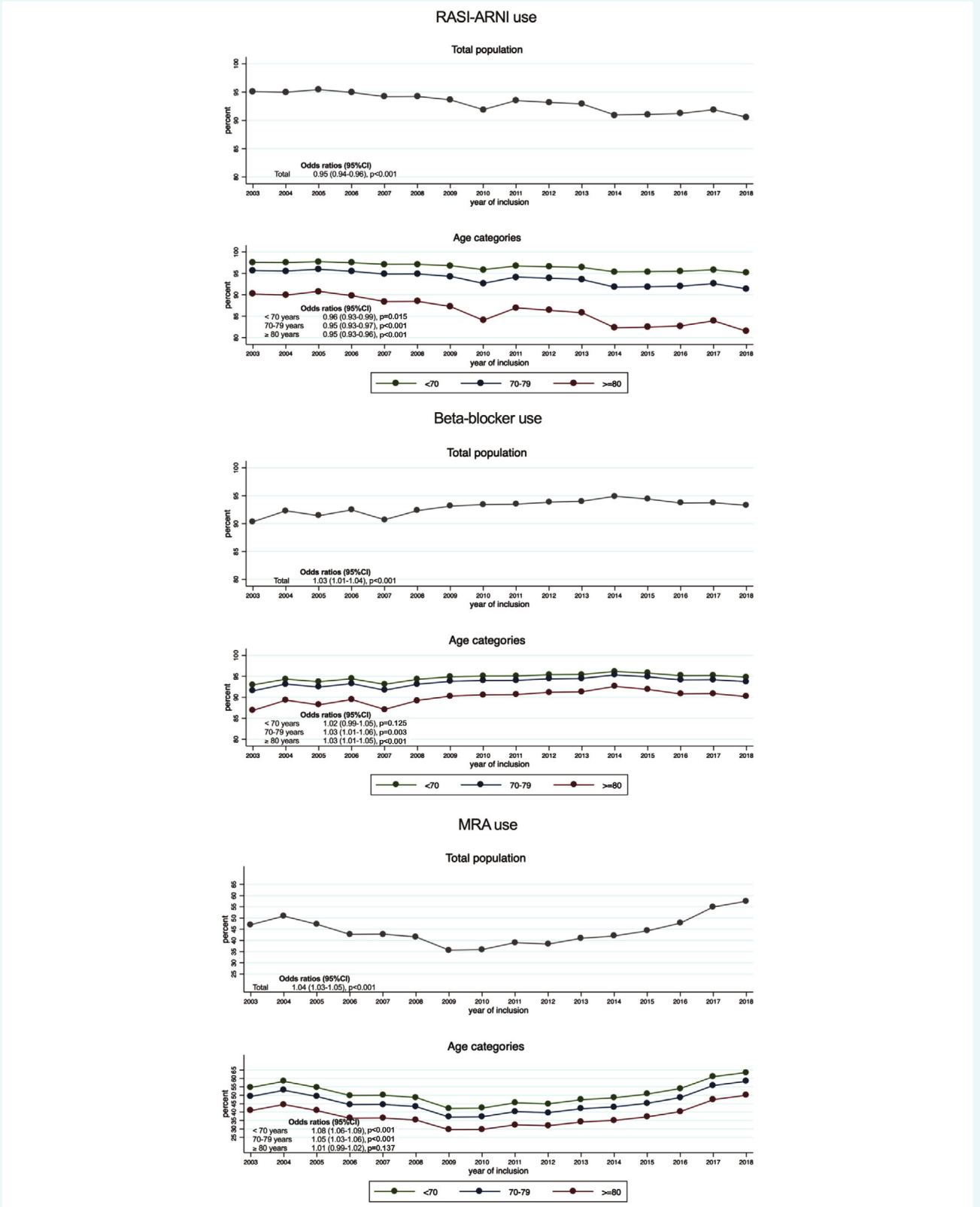


Figure 2 Temporal trends in the adjusted probability of guideline-directed medical therapy use in the overall cohort and across age strata. Trends in use of heart failure treatments start from 2003 when SwedeHF was implemented. ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; MRA, mineralocorticoid receptor antagonist; RASI, renin–angiotensin system inhibitor.

and *Figure S9*). Adjusted use of TD decreased over time regardless of age for RASI-ARNI, significantly increased in patients aged ≥70 years but not in those aged <70 years for beta-blockers, and significantly increased in patients aged <80 years but not in those aged ≥80 years for MRA (*Figure 3* and online supplementary *Table S10*).

Crude and adjusted use of ICD increased over time regardless of age. Crude use of CRT also increased over time regardless of age, whereas adjusted risk was overall stable in age ≥ 80 years, but increased and then decreased in age <80 years (*Figure 4*; online supplementary *Tables S9* and *S10*, *Figure S10*).

Discussion

In this national cohort of patients with HFrEF more than one-third were ≥80 years old, reinforcing the awareness that octogenarians do not represent a minority or a subgroup in real-world HF. The main findings of our analysis are as follows: (i) despite being more symptomatic, older (i.e. ≥80 years old) patients are less likely to receive guideline-recommended HF treatments including devices and TD of medications; (ii) with the exception of CRT, older age is independently associated with a lower probability of receiving guideline-recommended HF treatments; and (iii) these associations are consistent across several subgroups, but in the age stratum ≥80 years female sex is associated with a higher likelihood of treatment with RASI-ARNI, beta-blockers and MRA. Our results were obtained after comprehensive adjustment for patient characteristics (e.g. blood pressure, heart rate, potassium levels, renal function, non-cardiovascular comorbidities and markers of frailty) which might have otherwise justified overall non-use or non-achievement of TD (i.e. tolerability).

Use of heart failure treatments according to age

Age has been shown to be one of the major determinants of low prescription rates.[5–10] However, current guidelines do not report age-related differences in treatment strategies. The scarce enrolment of older patients in RCTs might be interpreted as limiting generalizability of the available evidence on tolerability and efficacy of GDMT to this patient group. However, in the SENIORS trial, the only RCT specifically designed to enrol a patient population ≥70 years old, beta-blockers reduced the risk of all-cause mortality/cardiovascular hospitalization, and in post-hoc analyses of RCTs on RASI and beta-blockers age did not impact the treatment effect, supporting the current statement from guidelines.[11,15,16] Previous observational studies from the SwedeHF Registry consistently showed a similar magnitude for the association between RASI and beta-blocker and mortality in older vs. younger patients, suggesting a significant survival benefit with these treatments regardless of age.[17,18]

In our cohort, 80% and 88% of patients ≥80 years old received RASI-ARNI and beta-blockers, respectively. Although octogenarians were less treated compared with patients <70 years old, we did report less underuse of RASI-ARNI and beta-blockers with older age in comparison with other studies.[7–10] Age-based differences in use of treatments were more evident for ARNI and MRA. A combination of RASI, beta-blockers and MRA was less used in patients aged ≥80 years compared to <70 years (26% vs. 50%), perhaps due to the perceived/actual higher exposure of older patients to adverse events or tolerability issues while on treatment with multiple drugs.

Of note, octogenarians were less likely treated compared with the youngest age stratum (<70 years), but this also applied to patients aged 70–79 years old in whom concerns regarding treatment tolerability and efficacy should be less. In older patients, uptitration of HF drugs may be difficult and in real-life care clinicians might be less committed to dosage maximization. In the CHAMP-HF registry, age was inversely associated with the likelihood of initiation or dose optimization of beta-blockers and ARNI, but not of RASI or MRA.[19] Similar findings for RASI and beta-blockers were observed in the BIOSTAT-CHF study and in the Euro Heart Failure Survey I and II,[5,8,20] whereas in a former European survey only beta-blockers were largely underused in older patients.[21] This is apparently in contrast with RCTs showing a comparable tolerability of beta-blocker TD in patients ≥65 vs. <65 years old.[22] At least two RCTs demonstrated that higher doses of RASI reduced HF hospitalizations compared with lower doses regardless of age, while for beta-blockers no difference in prognosis was observed for TD vs. intermediate doses in patients ≥70 years old.[5,11–14,23]

Use of heart failure devices according to age

The use of HF devices can be burdened by even lower adherence to guideline recommendations. In our study, the patterns of use were extremely divergent across age strata. ICD use was low in patients ≥80 years old (7%) but, after adjustments, both the age strata 70–79 years old and ≥80 years old reported lower odds for ICD implantation compared with age <70 years.

Post-hoc analyses of RCTs questioned the effect of primary prevention ICD on mortality in older patients due to the high risk of competing events,[24] but this finding has not been consistently observed.[25] Therefore, age *per se* should not be considered a contraindication to device therapies and, in absence of severe comorbidities, very advanced HF or frailty, the survival benefit may be still considerable.

A different use of CRT according to age has previously been reported, with some analyses highlighting higher likelihood of CRT implantation in older patients.[26] Beyond survival, with older age the improvement in symptoms and quality of life becomes a main target of treatments. In our cohort, after adjustments, age was not independently associated with CRT use, which is consistent with current evidence supporting efficacy also in older age.[26] This finding might also mirror a facilitated pharmacological treatment initiation/uptitration following CRT implantation in older patients. Consistently, in our analysis, CRT was independently associated with better pharmacological treatment in patients ≥70 but not <70 years old.

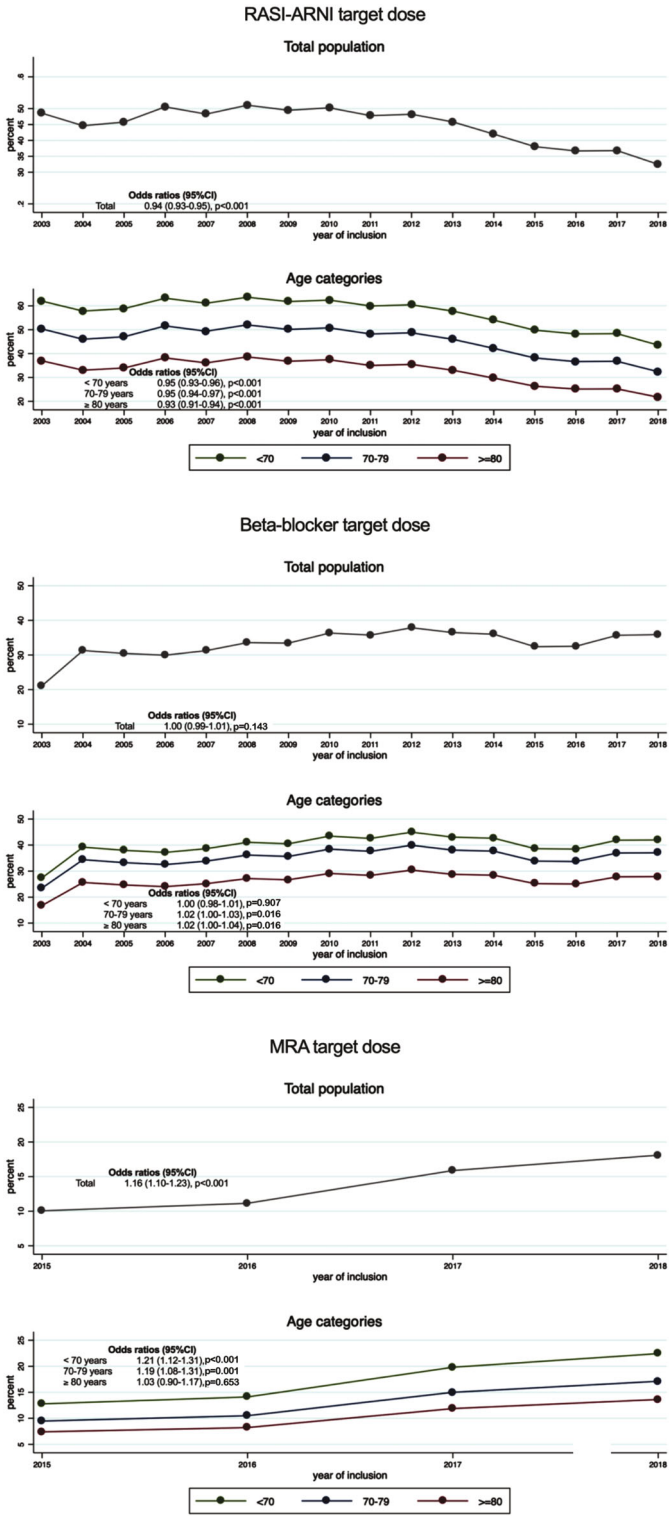


Figure 3 Temporal trends in the adjusted probability of target dose achievement of heart failure medications in the overall cohort and across age strata. Trends in use of heart failure treatments start from 2003 when SwedeHF was implemented; doses of mineralocorticoid receptor antagonists (MRA) were available from 2015. ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; RASI, renin–angiotensin system inhibitor.

[Correction added on 06 June 2022, after first online publication: Figures 3 and 4 were previously wrong and have been updated in this version.]

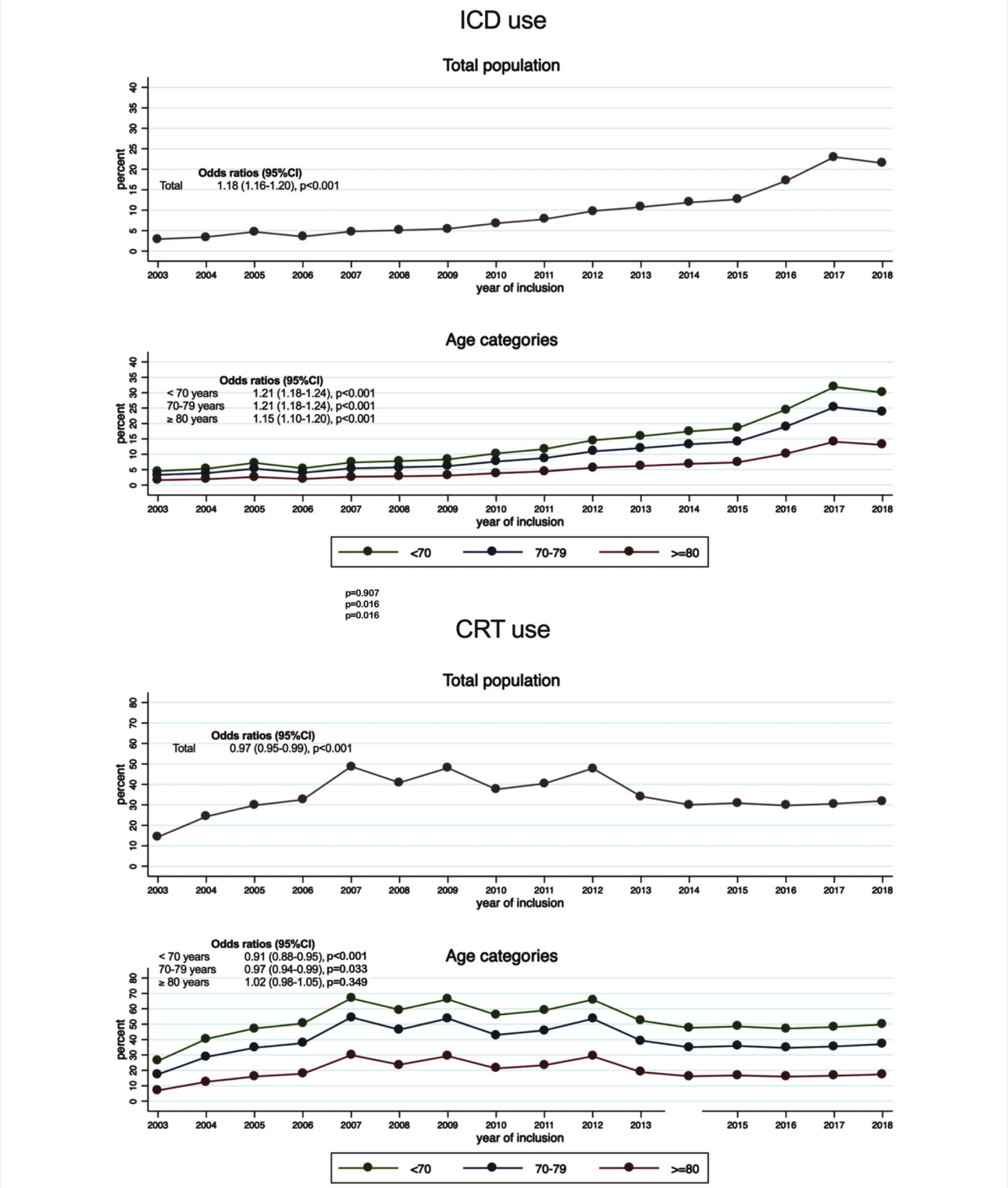


Figure 4 Temporal trends in the adjusted probability of heart failure device use in the overall cohort and across age strata. Trends in use of heart failure treatments start from 2003 when SwedeHF was implemented. CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

Age-related differences in use of heart failure treatments in specific subgroups and factors associated with GDMT use across age categories

In older patients, the reasons for underuse and underdosing are multiple and might include the burden of comorbidities that enhances the risk for adverse reactions. However, underuse of treatments in older patients with HF has been reported as independent of the comorbidity burden,[27] and among the potential reasons for the lower prescription rates there are the perception of low tolerance, the lack of knowledge/experience on how to manage and minimize adverse reactions, the limited awareness of the effects of therapies in older age categories, the patient preference and finally clinical inertia. In our study, we observed a concordant lower use/underdosing of HF treatments across most of the explored subgroups, and older age remained associated with lower use/underdosing of GDMT after extensive adjustments that also included markers of frailty and cognitive impairment (i.e. musculoskeletal/connective tissue diseases, dementia, depression). There were some sex-related disparities that differed based on age, with lower use of RASI in younger patients and of ARNI in older patients for females vs. males. In a previous European survey, ≥85-year-old females were more likely treated with RASI.[21] In our study, older age was independently associated with lower use of HF medications in males but not in females and, consistently, female sex was independently associated with more RASI-ARNI use in the age strata 70–79 and ≥ 80 years old, and with more beta-blocker and MRA use in patients ≥80 years old. This might be explained by sex-related differences in patient profiles. As previously shown in SwedeHF, among HFrEF patients females were older, had higher heart rate and blood pressure, more severe symptoms (i.e. NYHA class) and higher NT-proBNP.[28] We hypothesized that in the present study this might have promoted larger adoption of GDMT especially in older age strata, where females were more represented.

Recently, it has been proposed that females might benefit more than males from lower doses of HF medications.[29] In our study, the association between increasing age and lower TD achievement was consistent across sexes, and female sex was associated with lower TD achievement for RASI and beta-blockers in patients <70 years old and with lower TD achievement for beta-blockers in those ≥80 years old.

Impaired renal function, which is more frequent in older patients, might partially limit the use of HF medications. Consistently, we showed better renal function associated with higher use and dosing of RASI-ARNI and MRA. However, low eGFR should not be considered systematically as a contraindication to RASI which might improve prognosis also in patients with reduced renal function.[30] Hypo- rather than normo/hyperkalaemia was associated with underuse of RASI/ARNI and MRA across all age categories. The cross-sectional design of our study might explain this finding, with patients treated with RASI/ARNI and MRA reporting higher potassium levels compared with those untreated due to the actual use of the treatments.

In our study, older patients had higher blood pressure and were more likely treated with nitrates and diuretics. We found a significant association between blood pressure and underdosing but not with underuse of RASI-ARNI and beta-blockers, with no age-related differences. In older patients, maybe also due to the less likely referral to specialty care, symptomatic treatments are often preferred over therapies that improve prognosis,[7] and the fear that dose titration could lead to hypotension is stronger.

Other reasons for underuse and underdosing of HF treatments in older patients might be a lower socio-economic status, lower level of education, and less referral to specialty care. Consistently, in our analysis referral to primary rather than specialty care and no referral to nurse-led HF outpatient clinic were associated with underuse of treatments. Lower income and lower level of education were more likely to limit the use of devices vs. pharmacotherapy.

Temporal trends in use of guidelines-recommended heart failure therapies

In general, there were parallel temporal trends across age categories in the optimization of GDMT, including ARNI whose use increased from 5% in 2016 to 25% in 2018 (but less in older patients). However, there were age-related differences that became more evident after risk adjustments. The slight but significant decrease in use and full uptitration of RASI-ARNI was more evident in the ≥80-year age group and might find explanation in the enhanced attention to potential adverse events. Conversely, beta-blocker use in older patients significantly increased over time leading to reduce the gap with the younger group. Use of MRA overall increased after 2013 following the extension of the indications for MRA reported in the 2012 ESC guidelines, but not in older patients. The perceived higher risk of side effects and the more frequent follow-up in primary care are potential reasons for the lack of implementation of MRA use in older age. The rates of ICD implantation for primary prevention have instead shown a strong increase, particularly over the last 3 years, although with a less degree in patients ≥80 years old. On the other hand, despite the overall decrease in the adjusted likelihood of CRT implantation following the more stringent QRS duration criteria introduced in the 2016 ESC guidelines on HF,[2] use of CRT did not significantly change over time in older age categories, suggesting raised attention to the benefits of CRT with older age.

Limitations

Our observational registry-based study is subject to residual confounding and the specific reasons for not prescribing or not uptitrating therapies are not collected in the registry. However, our analyses were extensively adjusted for many potential reasons for underuse/underdosing/low tolerability including clinical (blood pressure, renal function, potassium, heart rate) and socio-demographic characteristics, and type of follow-up, which

might also be surrogates for the data that were missing. SwedeHF coverage is incomplete, thus selection bias may also be a limitation. QRS duration was not reported in SwedeHF before 2014 in patients with pacemaker (10.3% of the overall cohort), which might have potentially led to underestimating the number of patients with a potential indication for CRT in the earlier years. Adjustments for multiple comparisons were not performed, and therefore this should be taken into consideration when interpreting the results.

Conclusions

Contemporary treatment patterns in HFrEF still indicate gaps in the use of life-saving medications and devices. Guideline-recommended therapies were less used and less likely uptitrated with aging although currently recommended regardless of age. In older age categories, adherence to guideline recommendations was better in females. Improving strategies for better implementation of life-saving HF treatments and a more individualized approach might aid to improve morbidity and mortality in the overall HFrEF population, and is particularly needed in older patients, e.g. with more structured and stricter follow-up. Adequate representation of older patients in RCTs might support the implementation of treatment use in clinical practice.

Supplementary Information

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

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