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RESEARCH ARTICLE

Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry

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Aims To assess the association between combination, dose and use of current guideline-recommended target doses (TD) of renin–angiotensin system inhibitors (RASi), angiotensin receptor–neprilysin inhibitors (ARNi) and β-blockers, and outcomes in a large and unselected contemporary cohort of patients with heart failure (HF) and reduced ejection fraction.

Methods and results Overall, 17 809 outpatients registered in the Swedish Heart Failure Registry (SwedeHF) from May 2000 to December 2018, with ejection fraction <40% and duration of HF ≥90 days were selected. Primary outcome was a composite of time to cardiovascular death and first HF hospitalization. Compared with no use of RASi or ARNi, the adjusted hazard ratio (HR) (95% confidence interval [CI]) was 0.83 (0.76–0.91) with <50% of TD, 0.78 (0.71–0.86) with 50%–99%, and 0.73 (0.67–0.80) with ≥100% of TD. Compared with no use of β-blockers, the adjusted HR (95% CI) was 0.86 (0.76–0.91), 0.81 (0.74–0.89) and 0.74 (0.68–0.82) with <50%, 50%–99% and ≥100% of TD, respectively. Patients receiving both an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/ARNi and a β-blocker at 50%–99% of TD had a lower adjusted risk of the primary outcome compared with patients only receiving one drug, i.e. ACEi/ARB/ARNi or β-blocker, even if this was at ≥100% of TD.

Conclusion Heart failure with reduced ejection fraction patients using higher doses of RASi or ARNi and β-blockers had lower risk of cardiovascular death or HF hospitalization. Use of two drug classes at 50%–99% of TD dose was associated with lower risk than one drug class at 100% of TD.

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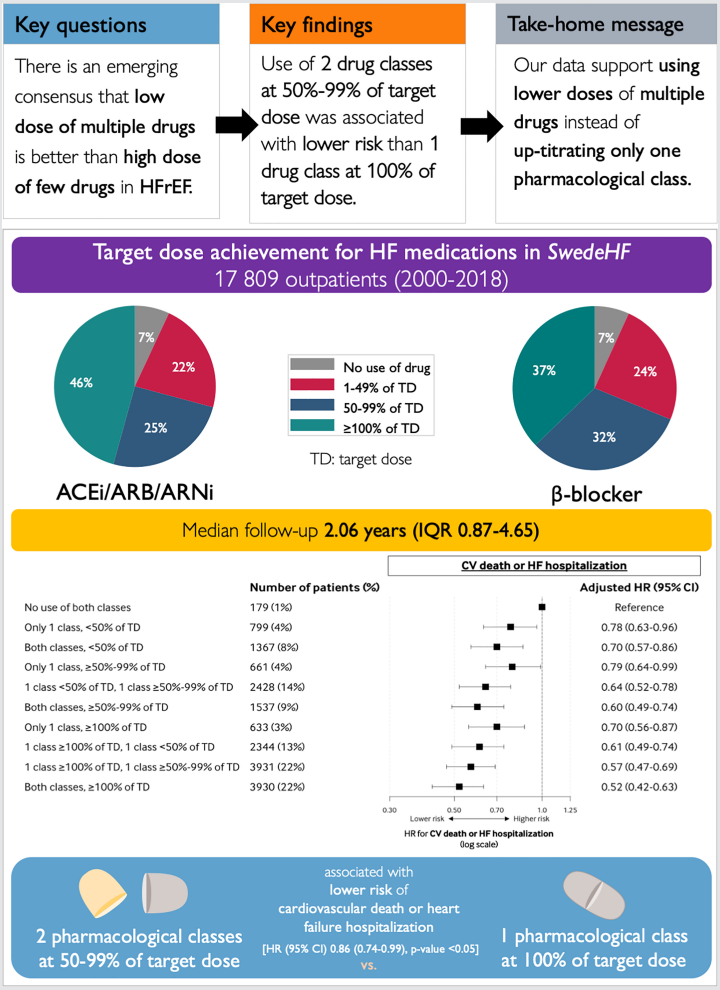
Graphical Abstract



In heart failure with reduced ejection fraction (HFrEF) lower doses of multiple drugs are associated with better outcome compared to one pharmacological class at optimal target dose (TD). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

Keywords Heart failure • Pharmacotherapy • Up-titration • Implementation

Introduction

Heart failure (HF) is a complex clinical syndrome associated with a heavy burden of symptoms, reduced quality of life, high mortality and morbidity, and high direct and indirect costs. Despite advancements in pharmacological and interventional therapies, the long-term outcome of patients with HF with reduced ejection fraction (HFrEF) remains poor.[1]

Neuro-hormonal modulators represent the cornerstone of HFrEF management. Over the last decades, several landmark randomized clinical trials adopting a strategy aiming for up-titration to target doses (TD) if tolerated showed a consistent reduction in morbidity and mortality.[2–8] Therefore, the 2016 European Society of Cardiology (ESC) guidelines on HF recommended using these treatments, with the traditional approach being a sequence of initiating and up-titrating one drug, followed by initiating and up-titrating the next drug, and so forth.[9]

Real-world data demonstrate a frequent undertreatment in terms of both number and doses of drugs indicated in HFrEF.[10–14] HFrEF drugs are also beneficial independent of one another,[15] and three randomized trials suggest that higher doses are more

effective than lower doses.[16–18] The 2021 ESC guidelines on HF suggest a rapid initiation of the four pillars of HFrEF pharmacotherapy, i.e. renin–angiotensin system inhibitors (RASi) or angiotensin receptor–neprilysin inhibitors (ARNi), β-blockers, mineralocorticoid receptor antagonists (MRA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), and only thereafter up-titrating to TD.[19] However, this new recommendation is supported by limited clinical evidence.

Thus, in a large real-world cohort of HFrEF patients, we explored the association between number and dosing of guideline-recommended drugs and mortality/morbidity in patients with HFrEF.

Methods

Design and setting

The Swedish HF Registry (SwedeHF; www.SwedeHF.se) has been previously described.[20] Inclusion criterion was clinician-judged HF until April 2017 and thereafter a diagnosis of HF according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, I13.2. Approximately 80 variables are recorded at discharge from hospital or after an outpatient clinic visit and entered into a web-based database managed by Uppsala Clinical Research Center (www.UCR.se).

Residents in Sweden have unique personal identification numbers enabling linking between population registries. For this analysis, SwedeHF was linked to the Cause of Death Registry, providing cause-specific mortality data, and the National Patient Registry (NPR), providing the outcome HF hospitalization and additional comorbidities. In the NPR, the positive predictive value for most diagnoses is between 85% and 95% and a HF diagnosis has been previously validated and verified in 86%–91% of cases.[21,22] Socioeconomic data were obtained by Statistics Sweden. Variables' description is reported in online supplementary *Table S1*.

Establishment of the HF registry and this analysis with the linkage of the above registries were approved by a multisite ethics committee.

Cohort selection

Outpatients registered in SwedeHF between 11 May 2000 (the start of the registry) and 31 December 2018, with ejection fraction <40%, duration of HF ≥90 days and no missing data for use and dose of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), ARNi and β-blockers were selected. A minimum HF duration of 90 days was chosen to take into account the time required for up-titration. Patients treated with an association of ARB and ACEi or ARNi, or with specific ARB or ACEi not recommended for HF treatment were excluded.[9,19] If the same patient had multiple registrations in SwedeHF, the last one was selected, since assumed more representative of contemporary care. *Figure 1* illustrates cohort selection.

Outcomes

The primary outcome was a composite of time to cardiovascular (CV) death and HF hospitalization (with censoring for non-CV death). Secondary outcomes were all-cause death and the individual components of the primary composite outcome (CV death with censoring for non-CV death; HF hospitalization with censoring at death). We also performed a sensitivity analysis investigating non-CV death (with censoring for CV death). Index date was defined as the day of the outpatient visit which led to registration in SwedeHF. Patients were followed up from index date to emigration from Sweden, death, 5 years from the index date, or end of follow-up (31 December 2018).

Statistical analysis

Patients who met the study selection criteria were divided into four categories according to the percentage of TD achieved for ACEi/ARB/ARNi and β-blocker (no use; <50% of TD; 50%–99% of TD; ≥100% of TD). TD were defined according to the 2016 and 2021 ESC guidelines on HF, as summarized in online supplementary *Table S2*.[9,19] If the guidelines reported a dose range, the lowest value of the range was conservatively chosen as target dose. Patients were also stratified into 10 groups according to the number of drugs used and the percentage of TD achieved for each of them, as shown in *Tables 1–3*. Consequently, the associations with outcomes of (i) different percentage of TD achievement for each drug; and of (ii) the combinations of different doses of ACEi/ARB/ARNi and β-blocker were assessed.

Continuous variables were reported as median and interquartile range (IQR), and categorical variables as counts and proportions (%). Baseline characteristics were assessed in the overall selected cohort and compared across the different dose categories for ACEi, ARB or ARNi and β-blocker, as well as across the combinations of different doses of ACEi/ARB/ARNi and β-blocker, using Kruskal–Wallis test for continuous variables and Pearson's chi-squared test for categorical variables.

Unadjusted survivor functions for use of ACEi, ARB or ARNi and β-blocker (separate and combined) were estimated using Kaplan–Meier method and compared across dose categories by log-rank test. Unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated fitting univariable and multivariable Cox proportional hazard models, respectively, for ACEi/ARB/ARNi and β-blocker, separately, and for the combinations of doses of ACEi, ARB or ARNi and β-blocker. The statistical interaction between category of TD achievement and period of registration as a categorical variable (index year <2006, 2006–2012, ≥2012) for the composite outcome of CV death and HF hospitalization and for all-cause death was tested using a Wald-type test. The proportional-hazards assumption was tested by assessing Schoenfeld residuals and met.

In multivariable models, missing data were handled by chained equation multiple imputation (10 imputed datasets generated). Variables included in multiple imputation model and multivariable analysis included category of TD achieved for ACEi/ARB/ARNi and β-blocker, along with demographics, organizational and socioeconomical characteristics (age, sex, year of registration, referral to HF nurse-led clinic, location of follow-up, education level, family type, disposable income), clinical characteristics (New York Heart Association [NYHA] class, ejection fraction, HF duration, heart rate, mean arterial pressure, weight), laboratory values (N-terminal pro hormone brain natriuretic peptide [NT-proBNP], estimated glomerular filtration rate [eGFR], potassium), comorbidities (history of hypertension, diabetes, smoking, prior myocardial infarction, coronary revascularization, atrial fibrillation, valve disease, anaemia, major bleeding, stroke or transient

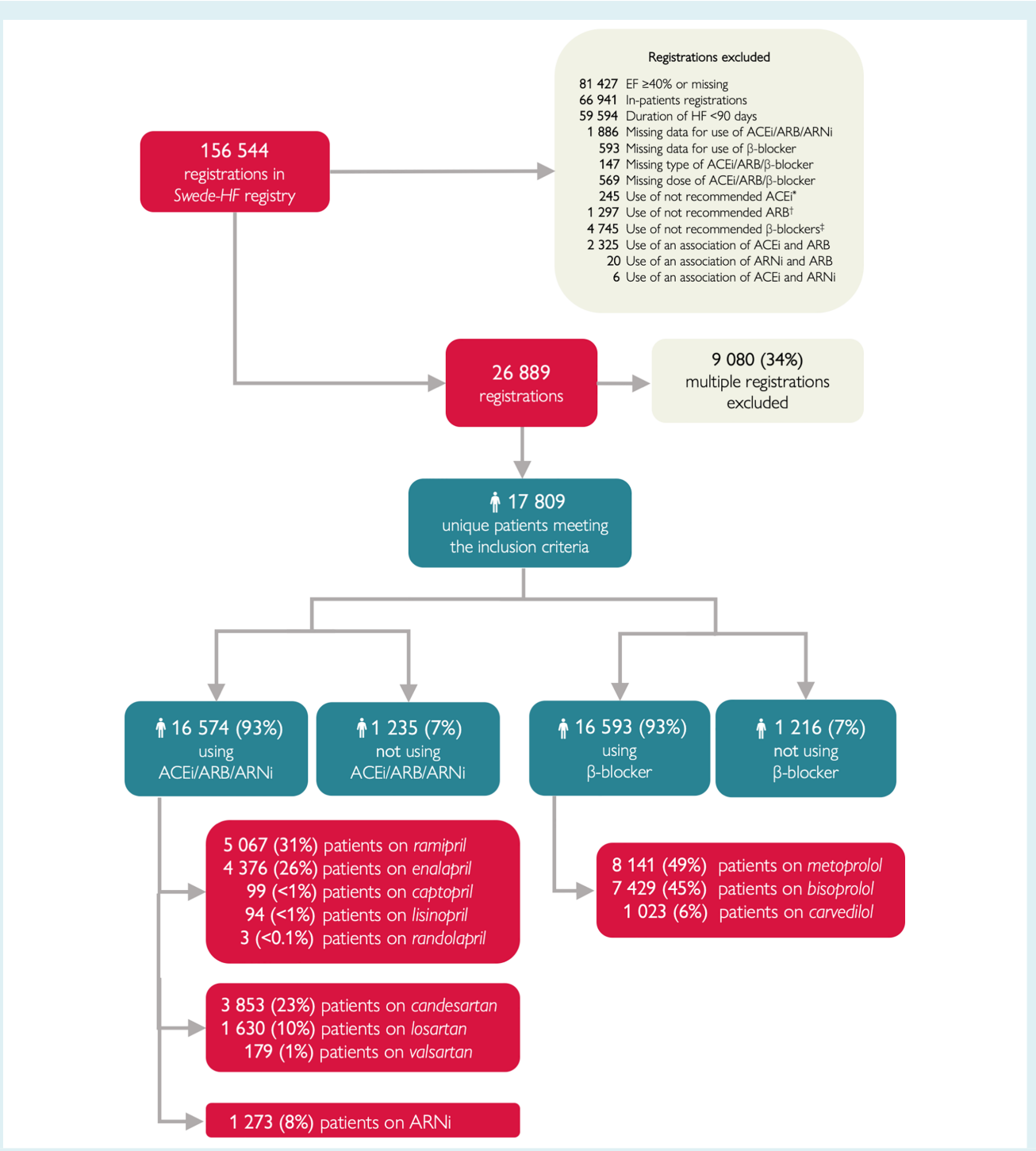


Figure 1 Flow chart describing cohort selection. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; HF, heart failure. *Cilazapril, fosinopril, kinapril, perindopril. †Eprosartan, irbesartan, telmisartan. ‡Atenolol, betaxolol, labetalol, pindolol, propranolol, sotalol, timolol.

ischaemic attack, peripheral artery disease, chronic obstructive pulmonary disease, liver disease, malignancies within 3 years), and other treatments (MRA, diuretics, digoxin, anticoagulants, antiplatelet agents, nitrate, statin, HF device). The primary outcome of CV death or HF hospitalization was included in the multiple imputation model as well. Percentage of missing data for each variable is shown in online supplementary *Table S3*.

Statistical analyses were performed using Stata version 16.1 (StataCorp, LLC, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

Table 1 Key baseline characteristics of patients categorized according to the percentages of target dose achievement for renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitor

Variables	No use (n = 1235, 6.9%)	1%–49% of TD (n = 3962, 22.2%)	50%–99% of TD (n = 4469, 25.1%)	≥100% of TD (n = 8143, 45.7%)	p-value
Demographics/organizational/socioeconomic					
Age (years), median (IQR)*	79 (72, 84)	76 (69, 82)	74 (67, 81)	71 (63, 78)	<0.001
≥75 years	814 (65.9%)	2279 (57.5%)	2182 (48.8%)	2960 (36.4%)	
Male sex	905 (73.3%)	2863 (72.3%)	3300 (73.8%)	6237 (76.6%)	<0.001
Year of registration					<0.001
2000–2005	44 (3.6%)	196 (4.9%)	134 (3.0%)	306 (3.8%)	
2006–2011	370 (30.0%)	1026 (25.9%)	1106 (24.7%)	2533 (31.1%)	
2012–2018	821 (66.5%)	2740 (69.2%)	3229 (72.3%)	5304 (65.1%)	
Location of follow-up					<0.001
Hospital	733 (62.9%)	2915 (75.7%)	3408 (78.1%)	6355 (79.9%)	
Primary care	405 (34.7%)	869 (22.6%)	903 (20.7%)	1488 (18.7%)	
Other	28 (2.4%)	67 (1.7%)	55 (1.3%)	109 (1.4%)	
Education					<0.001
Compulsory school	595 (49.1%)	1725 (44.2%)	1850 (42.2%)	3217 (40.1%)	
Secondary school	437 (36.1%)	1567 (40.2%)	1770 (40.4%)	3389 (42.2%)	
University	180 (14.9%)	608 (15.6%)	759 (17.3%)	1422 (17.7%)	
Living alone	614 (49.8%)	1772 (44.8%)	1972 (44.2%)	3509 (43.1%)	<0.001
Clinical					
NYHA class					<0.001
I–II	374 (36.6%)	1532 (43.5%)	2060 (51.7%)	4840 (65.7%)	
III–IV	648 (63.4%)	1989 (56.5%)	1923 (48.3%)	2531 (34.3%)	
Ejection fraction <30%	523 (42.3%)	1937 (48.9%)	2152 (48.2%)	3751 (46.1%)	<0.001
HF duration ≥6 months	1131 (91.6%)	3550 (89.6%)	3869 (86.6%)	6603 (81.1%)	<0.001
Heart rate (bpm), median (IQR)*	72 (64, 81)	70 (62, 80)	70 (62, 79)	68 (60, 76)	<0.001
MAP (mmHg), median (IQR)*	88 (80, 97)	83 (77, 93)	87 (78, 95)	90 (82, 98)	<0.001
BMI (kg/m^2), median (IQR)	25 (22, 29)	26 (23, 29)	27 (24, 30)	27 (24, 31)	<0.001
Laboratory values					
Haemoglobin (g/L), median (IQR)	128 (117, 140)	131 (120, 142)	134 (123, 145)	138 (127, 148)	<0.001
NT-proBNP (ng/L), median (IQR)*	4020 (1694, 9493)	2846 (1287, 6442)	2150 (876, 4610)	1539 (630, 3384)	<0.001
In sinus rhythm, median (IQR)	3177 (1218, 9015)	2085 (815, 5392)	1371 (567, 3638)	1040 (422, 2642)	
In atrial fibrillation, median (IQR)	4589 (2159, 9565)	3430 (1745, 7328)	2718 (1377, 5290)	2216 (1113, 4152)	
≥2070	482 (70.6%)	1458 (60.4%)	1415 (51.4%)	1867 (40.7%)	
eGFR (ml/min/1.73 m^2), median (IQR)*	42 (29, 59)	50 (37, 67)	57 (43, 75)	67 (52, 83)	<0.001
≥60 ml/min/1.73 m^2	285 (23.8%)	1316 (33.9%)	1961 (45.2%)	4895 (61.7%)	
Potassium (mEq/L), median (IQR)	4.2 (3.9, 4.5)	4.3 (4, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)	<0.001
History and comorbidities					
Hypertension	653 (54.9%)	1888 (49.0%)	2182 (50.2%)	3936 (49.6%)	0.004
Diabetes	382 (31.1%)	1078 (27.3%)	1269 (28.5%)	2051 (25.3%)	<0.001
Smoking					<0.001
Current	88 (9.0%)	314 (9.6%)	424 (11.7%)	893 (13.4%)	
Former	470 (48.1%)	1557 (47.6%)	1766 (48.7%)	3155 (47.3%)	
Never	419 (42.9%)	1403 (42.9%)	1440 (39.7%)	2622 (39.3%)	
Prior myocardial infarction	689 (55.8%)	2084 (52.6%)	2200 (49.2%)	3465 (42.6%)	<0.001
Coronary revascularization	450 (38.0%)	1542 (40.1%)	1664 (38.2%)	2689 (33.7%)	<0.001
Atrial fibrillation	694 (62.9%)	2161 (61.0%)	2293 (57.5%)	3700 (50.7%)	<0.001
Valve disease	344 (29.1%)	877 (22.7%)	852 (19.5%)	1255 (15.7%)	<0.001
Treatment					
β-blockers	1056 (85.5%)	3566 (90.0%)	4194 (93.8%)	7777 (95.5%)	<0.001
ACEi	0 (0.0%)	1571 (39.7%)	2326 (52.0%)	5742 (70.5%)	<0.001
Captopril	–	25 (1.6%)	54 (2.3%)	20 (0.3%)	
Enalapril	–	789 (50.2%)	1033 (44.4%)	2554 (44.5%)	
Lisinopril	–	12 (0.8%)	33 (1.4%)	49 (0.9%)	
Ramipril	–	745 (47.4%)	1206 (51.8%)	3116 (54.3%)	

Table 1 (Continued)

Variables	No use (*n* = 1235, 6.9%)	1%–49% of TD (*n* = 3962, 22.2%)	50%–99% of TD (*n* = 4469, 25.1%)	≥100% of TD (*n* = 8143, 45.7%)	*p*-value
Trandolapril	–	0 (0.0%)	0 (0.0%)	3 (0.1%)	
ARB	0 (0.0%)	2117 (53.4%)	1690 (37.8%)	1855 (22.8%)	<0.001
Candesartan	–	1133 (53.5%)	1058 (62.6%)	1662 (89.6%)	
Losartan	–	925 (43.7%)	567 (33.6%)	138 (7.4%)	
Valsartan	–	59 (2.8%)	65 (3.8%)	55 (3.0%)	
ARNi	0 (0.0%)	274 (6.9%)	453 (10.1%)	546 (6.7%)	<0.001
MRA	450 (36.5%)	1561 (39.5%)	2081 (46.6%)	4481 (55.2%)	<0.001
Diuretic (loop or thiazide)	1051 (85.2%)	3340 (84.5%)	3577 (80.1%)	5998 (73.8%)	<0.001
Loop diuretic[a]	756 (84.5%)	2434 (82.3%)	2687 (77.4%)	4159 (71.4%)	<0.001
Digoxin	177 (14.4%)	581 (14.7%)	630 (14.1%)	1153 (14.2%)	0.86
Statin	577 (46.8%)	2129 (53.8%)	2545 (57.1%)	4749 (58.4%)	<0.001
HF Device					<0.001
CRT-P	68 (5.6%)	200 (5.1%)	204 (4.6%)	314 (3.9%)	
CRT-D	84 (7.0%)	319 (8.2%)	409 (9.3%)	637 (7.9%)	
ICD	50 (4.1%)	282 (7.2%)	374 (8.5%)	624 (7.7%)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CRT, cardiac resynchronization therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro hormone brain natriuretic peptide.
[a]Data available starting June 1, 2010 on a total of 13 147 patients.

Results

Between 11 May 2000 and 31 December 2018, 156 544 entries were recorded in SwedeHF. Patients with multiple registrations were 5108 (28.7%), with 946 patients (5.3%) presenting more than three registrations. After selection of the last registration if multiple registrations were recorded, 17 809 outpatients with HFrEF (ejection fraction < 40%) and duration of HF ≥90 days, reporting data for use and dose of ACEi, ARB or ARNi and of β-blocker, were considered for this analysis (*Figure 1*).

Baseline characteristics

Baseline characteristics of the overall population are shown in online supplementary *Table S3* and the distribution of patients based on year of registration is shown in online supplementary *Figure S1*. The median age of the overall population was 74 years (IQR 65–80) and 75% were male. Patients using ACEi, ARB or ARNi were 93%, of which 58% on ACEi, 34% on ARB and 8% on ARNi. Patients using a β-blocker were 93%. Patients receiving both ACEi, ARB or ARNi and β-blocker were 87%.

Target dose achievement for separate drugs and their combination is shown in *Table 3*. Of patients receiving ACEi, ARB or ARNi, 24% received <50% of TD, 27% were treated with 50%–99% of TD, and 49% with a dose ≥100% of TD. Of patients receiving a β-blocker, <50% of TD was administered in 26%, 50%–99% of TD in 34%, and ≥100% of TD in 40%. As many as 22% received a dose ≥100% of TD of both ACEi/ARB/ARNi and β-blocker, whereas 3.5% received only one drug at a dose ≥100% of TD, 9% received both ACEi/ARB/ARNi and β-blocker at 50%–99% of TD, 8% received both treatments at <50% of TD, and 1% received none of these.

Tables 1, 2 and online supplementary *Table S4* summarize patient characteristics according to the percentage of TD achieved for RASi or ARNi and β-blocker. For both ACEi/ARB/ARNi and β-blocker, patients receiving a dose ≥100% of TD were younger, more likely to be planned for follow-up at specialty rather than in primary care, and to show characteristics reflecting less severe HF, i.e. lower NYHA class and lower NT-proBNP levels, higher eGFR, and lower comorbidity burden. Patients not receiving ACEi/ARB/ARNi or a β-blocker were older, had lower socioeconomical status (i.e. living alone, lower income, lower education level) and were more likely referred to primary care.

Online supplementary *Table S5* show baseline characteristics of patients receiving combinations of different doses of ACEi/ARB/ARNi and β-blocker. Notably, patients using a combination of RASi or ARNi and β-blocker at 50%–99% of TD were younger, more likely to be planned for follow-up at specialty rather than in primary care and to present characteristics reflecting less severe HF, i.e. lower NYHA class and lower NT-proBNP levels, as well as higher eGFR and preserved kidney function, compared with patients receiving only one pharmacological class at a dose ≥100% of TD.

Outcome analyses

Association between target doses of RASi or ARNi and outcomes

Median follow-up was 2.06 years (IQR 0.87–4.65). Compared with no use, each TD category of RASi or ARNi was associated with lower crude risk of CV death or HF hospitalization. With no use

Table 2 Key baseline characteristics of patients categorized according to the percentages of target dose achievement for β-blocker

Variables	No use (n = 1216, 6.8%)	1%–49% of TD (n = 4343, 24.4%)	50%–99% of TD (n = 5625, 31.6%)	≥100% of TD (n = 6625, 37.2%)	p-value
Demographics/organizational/socioeconomic					
Age (years), median (IQR)*	78 (70, 84)	76 (68, 82)	74 (66, 80)	71 (63, 78)	<0.001
≥75 years	742 (61.0%)	2379 (54.8%)	2628 (46.7%)	2486 (37.5%)	
Male sex	900 (74.0%)	3162 (72.8%)	4150 (73.8%)	5093 (76.9%)	<0.001
Year of registration					<0.001
2000–2005	76 (6.2%)	154 (3.5%)	229 (4.1%)	221 (3.3%)	
2006–2011	449 (36.9%)	1250 (28.8%)	1626 (28.9%)	1710 (25.8%)	
2012–2018	691 (56.8%)	2939 (67.7%)	3770 (67.0%)	4694 (70.9%)	
Location of follow-up					<0.001
Hospital	743 (63.1%)	3139 (74.3%)	4214 (77.1%)	5315 (82.2%)	
Primary care	411 (34.9%)	1010 (23.9%)	1176 (21.5%)	1068 (16.5%)	
Other	24 (2.0%)	75 (1.8%)	74 (1.4%)	86 (1.3%)	
Education					<0.001
Compulsory school	553 (46.2%)	1883 (44.2%)	2320 (42.0%)	2631 (40.2%)	
Secondary school	456 (38.1%)	1692 (39.7%)	2254 (40.8%)	2761 (42.2%)	
University	188 (15.7%)	683 (16.0%)	951 (17.2%)	1147 (17.5%)	
Living alone	573 (47.2%)	1947 (44.9%)	2522 (44.9%)	2825 (42.7%)	0.006
Clinical					
NYHA class					<0.001
I–II	524 (50.6%)	2087 (54.2%)	2719 (54.1%)	3476 (58.1%)	
III–IV	511 (49.4%)	1766 (45.8%)	2308 (45.9%)	2506 (41.9%)	
Ejection fraction <30%	505 (41.5%)	2038 (46.9%)	2619 (46.6%)	3201 (48.3%)	<0.001
HF duration ≥6 months	1070 (88.0%)	3719 (85.6%)	4759 (84.6%)	5605 (84.6%)	0.010
Heart rate (bpm), median (IQR)*	70 (61, 80)	68 (60, 76)	69 (60, 77)	70 (63, 80)	<0.001
MAP (mmHg), median (IQR)*	87 (78, 97)	87 (77, 94)	87 (79, 96)	90 (82, 97)	<0.001
BMI (kg/m^2), median (IQR)	25 (22, 29)	25.6 (23, 29)	26 (24, 30)	27 (24, 31)	<0.001
Laboratory values					
Hemoglobin (g/L), median (IQR)	132 (120, 143)	132 (121, 143)	134 (123, 145)	137 (125, 148)	<0.001
NT-proBNP (ng/L), median (IQR)*	2085 (840, 4680)	2137 (845, 4910)	2158 (869, 4810)	1940 (820, 4285)	0.026
In sinus rhythm, median (IQR)	1390 (563, 3375)	1555 (595, 3907)	1437 (558, 3610)	1188 (450, 3186)	
In atrial fibrillation, median (IQR)	2545 (1167, 5599)	2855 (1499, 6035)	2844 (1450, 5793)	2577 (1314, 5238)	
≥2070	322 (50.5%)	1336 (51.4%)	1674 (51.3%)	1890 (47.9%)	
eGFR (ml/min/1.73 m^2), median (IQR)*	57 (43, 74)	57 (42, 75)	59 (44, 77)	61 (45, 80)	<0.001
≥60	523 (44.2%)	1944 (45.7%)	2650 (48.3%)	3340 (51.9%)	–
Potassium (mEq/L), median (IQR)	4.3 (4, 4.5)	4.3 (4, 4.6)	4.3 (4, 4.6)	4.3 (4.1, 4.6)	<0.001
History and comorbidities					
Hypertension	540 (45.8%)	1911 (45.2%)	2717 (49.7%)	3491 (54.0%)	<0.001
Diabetes	276 (23.0%)	970 (22.4%)	1532 (27.3%)	2002 (30.4%)	<0.001
Smoking					<0.001
Current	82 (8.4%)	361 (10.2%)	579 (12.4%)	697 (13.0%)	-
Former	459 (47.2%)	1644 (46.4%)	2274 (48.8%)	2571 (47.8%)	-
Never	431 (44.3%)	1538 (43.4%)	1805 (38.8%)	2110 (39.2%)	-
Prior myocardial infarction	556 (45.7%)	2294 (52.8%)	2851 (50.7%)	2737 (41.3%)	<0.001
Coronary revascularization	386 (33.2%)	1636 (38.7%)	2175 (39.6%)	2148 (33.1%)	<0.001
Atrial fibrillation	618 (56.2%)	1835 (46.9%)	2713 (53.6%)	3682 (62.8%)	<0.001
Valve disease	269 (23.0%)	919 (21.7%)	1080 (19.6%)	1060 (16.3%)	<0.001
COPD	209 (17.2%)	558 (12.8%)	826 (14.7%)	917 (13.8%)	<0.001
Treatments					
β-blockers	0 (0.0%)	4343 (100.0%)	5625 (100.0%)	6625 (100.0%)	<0.001
Bisoprolol	–	1583 (36.4%)	2368 (42.1%)	3478 (52.5%)	
Carvedilol	–	274 (6.3%)	303 (5.4%)	446 (6.7%)	
Metoprolol	–	2486 (57.2%)	2954 (52.5%)	2701 (40.8%)	
ACEi	618 (50.8%)	2379 (54.8%)	3069 (54.6%)	3573 (53.9%)	<0.001

Table 2 (Continued)

Variables	No use (*n* = 1216, 6.8%)	1%–49% of TD (*n* = 4343, 24.4%)	50%–99% of TD (*n* = 5625, 31.6%)	≥100% of TD (*n* = 6625, 37.2%)	*p*-value
ARB	379 (31.2%)	1349 (31.1%)	1832 (32.6%)	2102 (31.7%)	0.036
ARNi	40 (3.3%)	212 (4.9%)	338 (6.0%)	683 (10.3%)	<0.001
MRA	465 (38.4%)	1836 (42.4%)	2634 (47.0%)	3638 (55.0%)	<0.001
Diuretic (loop or thiazide)	937 (77.3%)	3338 (77.0%)	4469 (79.6%)	5222 (78.9%)	0.009
Loop diuretic[a]	569 (74.1%)	2337 (73.6%)	3177 (77.4%)	3953 (77.6%)	<0.001
Digoxin	160 (13.2%)	401 (9.3%)	671 (11.9%)	1309 (19.8%)	<0.001
Statin	517 (42.6%)	2421 (55.8%)	3268 (58.2%)	3794 (57.3%)	<0.001
HF device					<0.001
CRT-P	39 (3.3%)	143 (3.3%)	257 (4.6%)	347 (5.3%)	
CRT-D	36 (3.1%)	225 (5.3%)	418 (7.5%)	770 (11.7%)	
ICD	32 (2.7%)	241 (5.6%)	425 (7.6%)	632 (9.6%)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro hormone brain natriuretic peptide.
[a]Data available starting June 1, 2010 on a total of 13 147 patients.

Table 3 Proportion of patients for percentage of target dose achieved and number of drugs in use

ACEi/ARB/ARNi	
No use of drug	7%
1%–49% of TD	22%
50%–99% of TD	25%
≥100% of TD	46%
β-blocker	
No use of drug	7%
1%–49% of TD	24%
50%–99% of TD	32%
≥100% of TD	37%
Combinations of ACEi/ARB/ARNi + β-blocker	
No use of both classes	1%
Only 1 class, <50% of TD	4%
Both classes, <50% of TD	8%
Only 1 class, ≥50%–99% of TD	4%
1 class <50% of TD, 1 class ≥50%–99% of TD	14%
Both classes, ≥50%–99% of TD	9%
Only 1 class, ≥100% of TD	4%
1 class ≥100% of TD, 1 class <50% of TD	13%
1 class ≥100% of TD, 1 class ≥50%–99% of TD	22%
Both classes, ≥100% of TD	22%

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; TD, target dose.

as reference, the unadjusted HR (95% CI) was 0.74 (0.68–0.80) with <50% of TD, 0.59 (0.54–0.64) with 50%–99% of TD, and 0.41 (0.38–0.45) with a dose ≥100% of TD (*Figure 2*, online supplementary *Table S6A*). Compared with ≥100% of TD, 50%–99% of TD was associated with a 41% higher risk of outcome (online supplementary *Table S6B*).

Consistently, after extensive adjustments, the risk of CV death or HF hospitalization for each category of TD achievement was lower compared with no use (HR [95% CI] 0.83 [0.76–0.91] with <50% of TD, 0.78 [0.71–0.86] with 50%–99% of TD, and 0.73 [0.67–0.80] with ≥100% of TD) (*Figure 3*, online supplementary *Table S6A*), with 50%–99% of TD vs. ≥100% of TD associated with 6% higher risk of outcome (online supplementary *Table S6B*).

Similar findings were observed for the outcomes of CV death and HF hospitalization, separately (online supplementary *Figures S2, S3*, *Table S6A,B*), and all-cause death (*Figure 3*, online supplementary *Table S6A,B*), as well as non-CV death (online supplementary *Table S6C*).

The interaction between achievement of TD for RASi or ARNi and period of registration was not statistically significant for the primary outcome of CV death and HF hospitalization (*p*-interaction 0.92), as well as for all-cause death (*p*-interaction 0.92).

Association between target dose of β-blocker and outcomes

The crude HR (95% CI) for the association between CV death or HF hospitalization and percentage of TD achievement of β-blocker was 0.86 (0.78–0.94) with <50% of TD, 0.80 (0.73–0.87) with 50%–99% of TD, and 0.67 (0.61–0.73) with a dose ≥100% of TD compared with no use (*Figure 2*, online supplementary *Table S6A*), and with a 19% statistically significant higher risk of outcome with use of 50%–99% of TD versus ≥100%, highlighting lower risk of outcome associated with higher TD achievement (online supplementary *Table S6B*).

Consistent findings were again observed after extensive adjustments: HR (95% CI) was 0.86 (0.79–0.95) with <50% of TD, 0.81 (0.74–0.89) with 50%–99% of TD, and 0.74 (0.68–0.82) with a dose ≥100% of TD, compared with no use (*Figure 3*, online supplementary *Table S6A*). A dose 50%–99% of TD versus ≥100% was associated with 9% higher risk of outcome (online supplementary *Table S6B*).

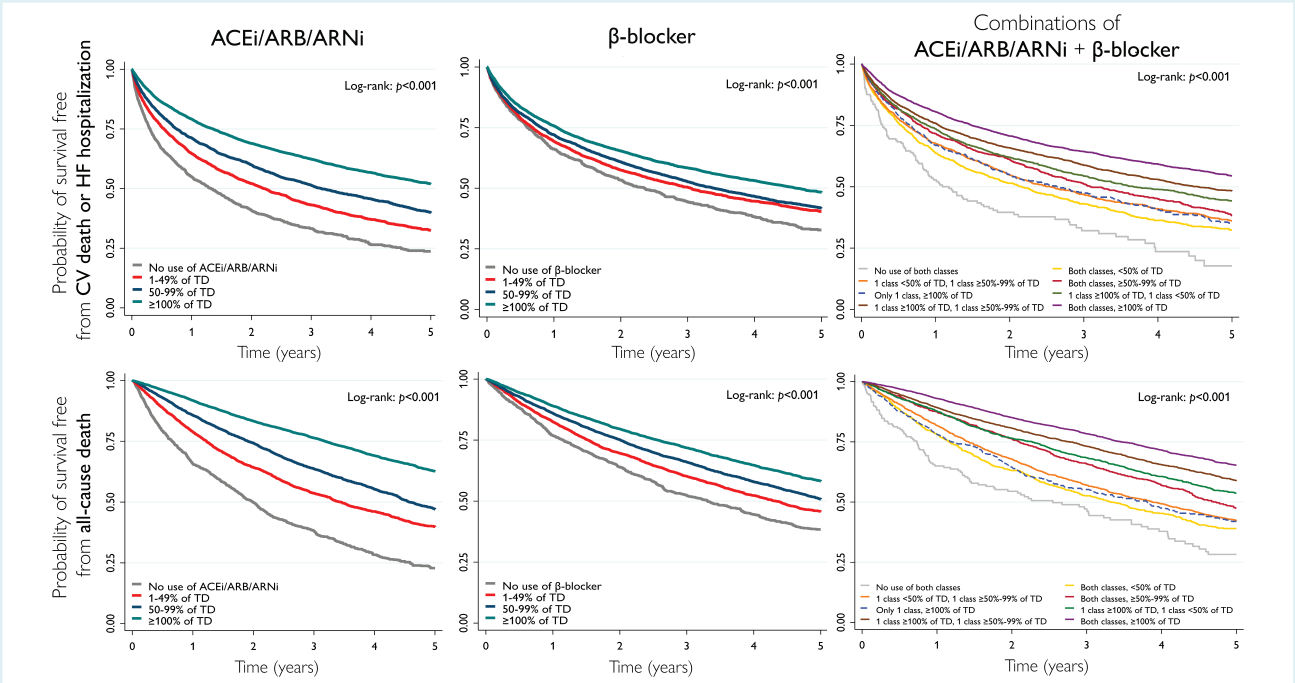


Figure 2 Kaplan–Meier curves for the risk of cardiovascular death or heart failure hospitalization and of all-cause death according to the percentage of target dose achieved per class of drug and their combination. Categories of monotherapy <100% of target dose not shown because of the very low number of observations, but included in the long-rank test. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HF, heart failure; TD, target dose.

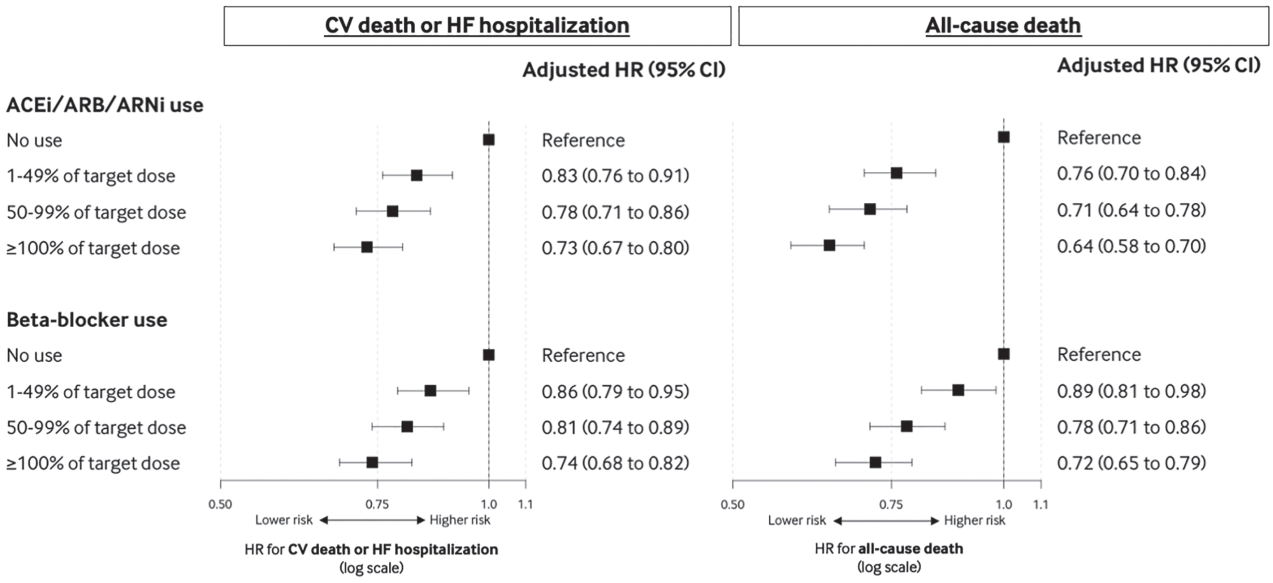


Figure 3 Independent associations of the percentages of target dose achieved per class of drug with the composite outcome of cardiovascular death or heart failure hospitalization and with all-cause death. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HF, heart failure; HR, hazard ratio; TD, target dose.

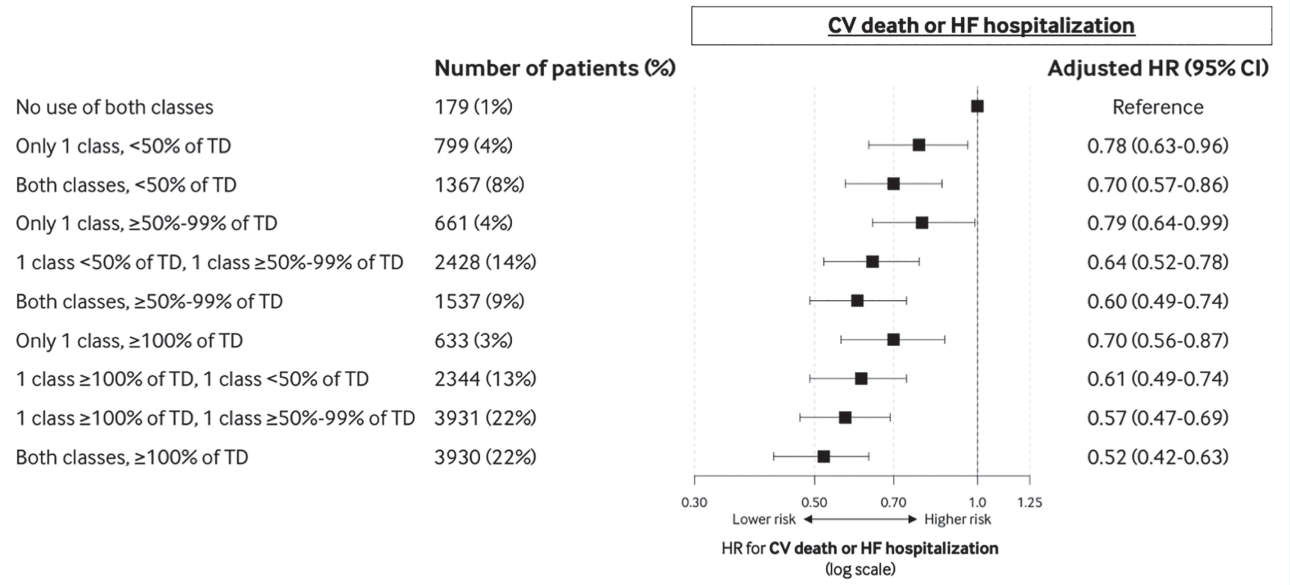


Figure 4 Independent associations of the different combinations of target dose achievement for renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitor and β-blocker with the composite outcome of cardiovascular death or heart failure hospitalization. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HF, heart failure; HR, hazard ratio; TD, target dose.

Similar associations were observed between the percentage of TD achievement and the risk of CV death and HF hospitalization, separately (online supplementary *Figures S2, S3*, *Table S6A,B*), and all-cause death (*Figure 3*, online supplementary *Table S6A,B*). In adjusted analysis, only patients achieving a dose ≥100% of TD showed lower risk of non-CV death compared with no use of β-blocker, while the risk of non-CV death of patients using 50%–99% of TD versus ≥100% was comparable (online supplementary *Table S6C*).

The interaction between achievement of TD for β-blocker and period of registration was not statistically significant for the primary outcome of CV death and HF hospitalization (*p*-interaction 0.47), as well as for all-cause death (*p*-interaction 0.32).

Association between combinations of different doses of RASi/ARNi and β-blocker with outcomes

Unadjusted analyses are reported in *Figure 2*, and online supplementary *Table S7* and *Figure S4*.

As shown in *Figure 4*, when compared with no use of either RASi/ARNi or β-blocker, patients receiving ≥100% of both RASi/ARNi and β-blocker showed the lowest adjusted risk of CV death or HF hospitalization (HR (95% CI) 0.52 [0.42–0.63]) (online supplementary *Table S7A*). Use of only one pharmacological class at ≥100% of TD versus a combination of both drugs at ≥100% was associated with a 35% higher risk of outcome (online supplementary *Table S7B*). Notably, the adjusted risk of outcome with a combination of RASi or ARNi and β-blocker at 50%–99% of TD was 14% lower compared with the use of only one pharmacological class at a dose ≥100% of TD (HR (95% CI) 0.86 [0.74–0.99]).

Consistent results were observed for CV death or HF hospitalization, separately, and all-cause death (online supplementary *Figures S4, S5*). After adjustments, only patients using both drugs at a dose ≥100% of TD had lower risk of non-CV death compared with no use of any drug (online supplementary *Table S7C*).

The interaction between combinations of different doses of RASi/ARNi and β-blocker and period of registration was not statistically significant for the primary outcome of CV death and HF hospitalization (*p*-interaction 0.81), as well as for all-cause death (*p*-interaction 0.95).

Discussion

We explored the use of number and dose of recommended HFrEF medications and their association with prognosis in a large, unselected and contemporary cohort of patients with chronic HF. We confirmed that use of RASi/ARNi plus β-blocker is high but that underdosing is common, with less than 50% of patients receiving recommended TD of each of these drug classes and less than 25% receiving TD of both classes. After extensive adjustments, increasing percentage of TD achievement of RASi/ARNi and β-blocker was associated with lower risk of CV death and HF hospitalization, as well as of all-cause mortality, and with the lowest risk in patients receiving TD.

Given the recommendation of combining RASi or ARNi with a β-blocker, we assessed use and association with outcomes of different combinations of doses of these pharmacological classes. The lowest adjusted risk of CV death or HF hospitalization was observed with use of both ACEi/ARB/ARNi and β-blocker at a

dose ≥100% of TD, which was 48% lower compared with no use of drugs. Notably, a dual drug approach with RASi or ARNi with a β-blocker at a dose 50%–99% of TD was associated with a 14% lower adjusted risk of CV death or HF hospitalization compared with monotherapy at a dose ≥100% of TD. These findings support the emerging consensus and the 2021 ESC guidelines on HF recommending initiation of multiple drugs prior to up-titrating each one.[15,19,23]

Evidence from trials on the need of up-titrating heart failure medications

There is a small number of trials comparing higher versus lower doses of HF medications. They were performed more than 10 years ago when HFrEF medications were fewer, and therefore the benefit of achieving TD might have been greater than in contemporary HF care characterized by polypharmacotherapy. The Multicenter Oral Carvedilol HF Assessment (MOCHA) trial suggested a beneficial relationship between use of higher carvedilol dose and mortality,[18] and a post-hoc analysis of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial showed an inverse relationship between β-blocker dose and all-cause death or all-cause hospitalization.[24] Similarly, data comparing RASi doses are few.[16,17,25–28] High (32.5–35 mg) versus low dose (2.5–5 mg) of lisinopril was associated with lower risk of all-cause death and HF hospitalization in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial,[16] and high dose (150 mg) versus low dose (50 mg) of losartan led to lower risk of all-cause death and HF hospitalization in the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study.[17] A meta-analysis of six trials showed that high versus low doses of RASi only modestly reduced all-cause mortality and HF hospitalization without increasing drug discontinuation rates.[29]

Up-titration of heart failure medication and its associations with outcomes in real-world care

In spite of this body of evidence supporting up-titration to the maximum tolerated dose, the degree of TD achievement in real-world clinical practice is low. In our registry-based study, the proportion of patients using TD of RASi or ARNi and β-blocker was higher than in other international cohorts. Namely, we found that TD of β-blocker was administered in 37% of patients, whereas it was 19% in the Dutch CHECK-HF registry (2013–2016),[11] 17.5% in the ESC Heart Failure Long-Term Registry (2011–2013),[10] 16% in the Quality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure survey (QUALIFY) global study (2013–2014)[12] and 27.5% in the Change the Management of Patients with Heart Failure (CHAMP-HF) study (2015–2017) from the US.[13] In SwedeHF, 46% of patients received TD of RASi or ARNi, which was 44% in CHECK-HF,[11] 38% in QUALIFY,[12] 28% in the ESC Heart Failure Long-Term Registry,[10] and 17% in the CHAMP-HF registry.[13] In Asia, the ASIAN-HF registry (2012–2015) showed rates of TD achievement similar to those observed in the US, i.e. 17% for RASi and 13% for β-blocker.[14] Different study designs, enrolment settings (e.g. primary vs. secondary vs. tertiary care), and health care systems might contribute to explain the differences in TD achievement reported across these studies. However, patient profiles associated with TD achievement were consistent across previous studies and our analysis in SwedeHF, i.e. younger age, male sex and less comorbidity burden as key determinants. Patients receiving suboptimal drug therapy had lower socioeconomical status, an observation which expands previous evidence on less use of recommended treatments in these patients[30] and which also warrants further investigation on possible implementation of socioeconomic interventions in order to improve therapy optimization. Importantly, randomized trials showed in general higher TD achievement, i.e. at least 50%–60%,[3,4,6,8,31–33] which is likely explained by the stricter inclusion criteria of clinical trials, aiming to exclude older patients and multicomorbid patients.[34]

Our outcome analysis partially confirms and expands previous observations.[14,35] We found lower risk of CV death or HF hospitalization, CV death or HF hospitalization, separately, and of all-cause mortality with ≥100% versus 50%–99% of TD of RASi or ARNi. In a smaller and prospective but also observational cohort, the BIOSTAT-CHF study (2010–2012), patients receiving RASi at ≥100% of TD showed only a trend toward risk reduction of all-cause death and/or HF hospitalization comparable to those receiving 50%–99% of TD,[35] which might be at least partially explained by power issues. In the prospective ASIAN-HF registry (2012–2015), patients receiving RASi at 50%–99% of TD had a lower adjusted risk of a 1-year composite outcome of all-cause death and HF hospitalization compared with patients achieving 100% of TD.[14] Different degrees of adjustment for HF severity, with physicians tending to up-titrate treatments in patients with more severe HF, might contribute to explain the differences in results across the available studies. However, in both these previous studies, the magnitude of association with all-cause death and HF hospitalization increased together with the achievement of a higher percentage of TD for β-blocker, which is consistent to what we observed in SwedeHF. Notably, in our study 49.6% of patients using a β-blocker had concomitant atrial fibrillation. Current guidelines recommend a β-blocker regardless of heart rhythm, but evidence on the prognostic benefits with β-blockers in patients with atrial fibrillation is controversial.[36,37]

Low tolerance issues linked with an overall worse clinical status impact drug initiation and TD achievement, and is common in clinical practice. Post-hoc analyses of the Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial reported that older age, lower systolic blood pressure, more severe symptoms of HF, and worse renal function were predictors of discontinuation during the run-in period and of any dose reduction thereafter, and that patients experiencing any dose reduction were at higher risk of CV death or HF hospitalization.[38,39] Since in our study the observed association between higher TD dose achievement and better prognosis might be at least in part explained by the overall worse clinical profile in those receiving lower doses due to tolerability issues,

we performed extensive adjustment for 41 variables (i.e. sociodemographic, organizational and clinical characteristics, comorbidities, and treatments), including key patient characteristics affecting drug tolerability (e.g. age, comorbidity, heart rate, blood pressure, kidney function, potassium) or mirroring a more advanced HF (NT-proBNP, NYHA class, HF duration, ejection fraction). However, treatment effects can be assessed only by randomized clinical trials since observational studies as ours, even if adopting extensive adjustments, cannot rule out unmeasured and unknown confounding and selection bias,[40] and therefore these results need to be interpreted accordingly.

Multitherapy at lower doses versus monotherapy at target dose

Data on the frequency of use and the risk of outcomes associated with monotherapy versus multitherapy with RASi/ARNi and β-blocker at different percentages of TD are even more limited. In HFrEF trials, drugs were added on top of standard of care, and benefits were additive and independent of one another.[19] Most of the landmark trials testing the benefit of β-blockers vs. placebo had ACEi as a background therapy, and the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III trial highlighted that bisoprolol-first versus enalapril-first sequencing strategy are both safe and effective.[41] Following meta-analyses of randomized clinical trials and an estimation of life-years gained with incremental therapies in BIOSTAT-CHF and ASIAN-HF suggest that current recommended drugs might have additive prognostic benefits.[42–44]

Previous guidelines recommended a sequential order of initiation–up-titration of treatments, which reflected the timing of their testing in randomized controlled trials and introduction in HF care.[9] Cons of this approach were that a slow up-titration phase might have delayed or even prevented the introduction of life-saving therapies listed as second or third-line treatment in the therapeutic algorithm.[45] Additionally, a sequential up-titration to maximal tolerated doses in patients experiencing tolerability issues may also contribute to delay initiation of multiple drugs.[46] Based on this background, the 2021 ESC guidelines on HF recommend in all HFrEF patients a rapid and early initiation of the four pillars of HFrEF pharmacotherapy and only thereafter up-titration to target doses without any sequential approach but according to the specific patient profile.[19,46] However, evidence on the prognostic benefits linked with the use of more drugs at lower dose versus less drugs at higher dose is limited, and might be key to drive the initiation and optimization of HF pharmacotherapy in these patients.

In our study, patients on monotherapy with RASi or ARNi or β-blocker were ~12%, whereas patients receiving both RASi or ARNi and β-blocker at TD were ~22%. We showed better outcome in patients receiving ≥100% of TD of both RASi/ARNi and β-blocker, similar to what was observed in the BIOSTAT-CHF study, which compared only dual therapy with ACEi and β-blocker at different percentages of TD versus no use of drugs.[35] A novel finding in our study was that patients receiving both RASi/ARNi and β-blocker at 50%–99% of TD had better prognosis compared to those receiving only one of these drugs at ≥100% of TD. These data highlight that a sequential approach where a new drug is introduced once that the others have been up-titrated at TD might not be the best and might limit the simultaneous use of the four pillars of HFrEF pharmacotherapy. Therefore, our findings are in agreement with the new 2021 ESC guidelines on HF and the American College of Cardiology Expert Consensus Decision Pathway for HF therapies, which advice the use of lower doses of multiple drugs instead of only one pharmacological class at maximum dose in the presence of tolerability issues.[19,47] Although enforcing the concept that an early combination therapy is important, our analysis also highlights that dosing still remains a key issue and efforts must be put in promoting up-titration to maximum tolerated doses according to specific patients' profiles as soon as the treatment with all the pillars of HFrEF pharmacotherapy has been initiated.[48]

Limitations

One strength of our study is the use of the SwedeHF registry providing a real-world HFrEF population, which is larger, has longer follow-up and is less selective compared with previous observational studies enrolling ad-hoc cohorts with the purpose of investigating implementation of HF therapies.[11–13,35]

Specific reasons which might justify non-use or lack of up-titration are not reported in the registry. It is therefore possible that both use of higher doses and greater number of drugs are affected by unmeasured confounders, e.g. limited tolerability to treatments. However, the decision to up-titrate one drug instead of first adding another drug is less likely to be confounded, since this would be less affected by patient or provider characteristics. We observed that using a dose ≥100% of TD was also associated with lower risk of non-CV death. This warrants caution on reverse causation, because patients with lower risk of non-CV death might have been more likely to receive optimized use of and better tolerate HF medications.

Patients were registered between 2000 and 2018, i.e. a long period which has seen important improvements in HFrEF therapy. While adjustment for and test of statistical interaction with year of registration have been performed, evolving standards of care and the possibility that drug doses might have been up-titrated later than at our assessment should be taken into account.

We studied RASi/ARNi and β-blockers but we planned not to include an assessment of MRA use/dose alone and in combination with the other drugs, since MRA use is particularly prone to indication bias in our registry setting considering data collected during a time period when guidelines recommended MRA use in patients with more severe HF.[49] Additionally, dose was missing in ~40% of patients using MRA and, whenever registered, 50% of TD was administered in more than 70% of patients receiving this class of medication. Also, even though SGLT2i were used during the later years of the inclusion period, they were not yet indicated in HF and are not dose-titrated.

Additionally, due to the cross-sectional assessment of drug doses we could not investigate the different patterns of titration, while sequencing and dosing of RASi, ARNi and β-blocker may have varied across patients before the establishment of the therapy that we assessed. We also categorized combinations of doses/therapies

without accounting for the specific drug type used for each dose range, whereas this might be relevant to inform how deciding which drug to up-titrate first.

We selected only registrations of patients with available data on treatment use and dose, which could have led to biased estimates, with underrepresentation of patients not receiving or receiving poorly up-titrated treatments. However, this might have led to the exclusion of patients with worse prognosis and therefore to underestimate the magnitude of the observed associations. There were also some missing data for other variables considered for adjustments, which we handled by multiple imputation to increase external validity.

Around 29% of patients had multiple registrations, and we cross-sectionally defined last registration as index visit, since assumed to be more representative of contemporary care. However, patients with better outcomes and longer survival may have had longer time to get a repeated visit and achieve up-titration of treatments (survival bias), but – on the contrary – deteriorating patients may also have had a greater indication for a repeated visit and possibly earlier treatment intensification. Although we cannot rule out such bias, this should affect outcomes in opposite directions.

Finally, SwedeHF coverage is not complete, i.e. ~30% in 2019. Patients enrolled in this registry have been previously shown to be more likely male and younger, and better treated than the overall Swedish HF population.[50] Additionally, most of our study population was enrolled in secondary versus primary care. Therefore, the generalizability of our findings should be interpreted accordingly.

Conclusions

Use of target doses of RASi or ARNi and β-blockers was associated with lower risk of CV death or HF hospitalization and of all-cause death in patients with HFrEF. A dual drug approach with RASi or ARNi and β-blockers at a dose 50%–99% of TD was associated with better outcome compared with the use of only one drug, even at a dose ≥100% of TD. Our data support the current guideline recommendation of using first lower doses of multiple drugs instead of up-titrating only one pharmacological class.

Supplementary Information

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

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