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ORIGINAL RESEARCH

Adherence and Discontinuation of Optimal Heart Failure Therapies According to Age: A Danish Nationwide Study

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BACKGROUND: Guideline-recommended disease-modifying pharmacological therapies for heart failure (HF) with reduced ejection fraction are underutilized, particularly among elderly patients. We studied the association of age in adherence and discontinuation of angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers (ACEi/ARB), β-blockers (BB), and mineralocorticoid receptor antagonists.

METHODS AND RESULTS: Patients with a first heart failure diagnosis who had initiated ACEi/ARB and BB within 120 days of presentation were included from nationwide registries and divided into 3 age groups: <65 years (reference), 65 to 79, and ≥80. One-year median proportions of daily target doses were calculated. Adherence was estimated by the proportion of days covered. The 5-year risk of discontinuation was assessed with the Aalen-Johansen estimator. Discontinuation rates were evaluated using Multivariable Cox regression. Twenty-nine thousand four hundred eighty-two patients were included. Advancing age was associated with lower median proportions of daily target doses and adherence (ACEi/ARB 79.1%, 77.5%, and 69.4%; BB 79.1%, 78.6%, and 73.8%), in the <65, 65 to 79, and ≥80 age groups, respectively. Age ≥80 was associated with higher discontinuation rates (cumulative incidence, ACEi/ARB 41%, 44%, and 51%; BB 38%, 35%, and 39%; hazard ratio, ACEi/ARB 1.60 [95% CI, 1.51–1.69]; BB 1.33 [95% CI, 1.25–1.41]). The risk of mineralocorticoid receptor antagonists discontinuation differed little with age (50%, 54%, and 56%), although mineralocorticoid receptor antagonists initiation in the most elderly was less frequent (33%, 33%, and 22%).

CONCLUSIONS: In a nationwide cohort of patients with heart failure, advanced age was associated with lower proportions of daily target doses, lower adherence, and higher discontinuation rates of ACEi/ARB and BBs. Focus on treatment adherence and optimal dosages among elderly patients with heart failure could improve outcomes.

Key Words: adherence ■ age ■ discontinuation ■ heart failure ■ pharmacotherapy

Pharmacological therapy for heart failure (HF) has improved significantly over recent decades, and care is increasingly delivered by multiprofessional teams and in specialist clinics.[1] Until recently, first-line treatment consisted of pharmacotherapy with an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin-II receptor blockers (ARB), and a β-blocker (BB), with the addition of a mineralocorticoid receptor antagonist (MRA) in patients with persisting symptoms and low ejection fraction.[1] Angiotensin receptor neprilysin inhibitors sacubitril/valsartan and the sodium-glucose co-transporter 2 inhibitors are the newest pharmacological strategies in HF and have been shown to have additional benefits.[2,3] However, the potential addition of these new therapies

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CLINICAL PERSPECTIVE

What Is New?

- Very elderly patients (aged ≥80 years) on guideline-directed medical therapy for heart failure received lower drug doses, had lower adherence, and significantly higher discontinuation rates than younger patients.

What Are the Clinical Implications?

- In real-life practice, a more comprehensive approach to elderly patients with heart failure is needed to improve adherence and prevent discontinuation of vital pharmacotherapies where appropriate.

Nonstandard Abbreviations and Acronyms

BB	β-blocker
MRA	mineralocorticoid receptor antagonist

has raised concerns about medication adherence and treatment discontinuation among patients with HF who are often on many other drugs.[4] This is especially true among elderly patients, who constitute a large part of the general HF population, and who are generally underrepresented in clinical trials, making them an important but overlooked patient group, and leaving uncertainty about the applicability of guideline-directed HF therapies when treating these patients.

The impact of aging on adherence and discontinuation in HF is unclear.[5,6] Thus, to quantify the significance of advancing age—particularly focusing on the most elderly ≥80 years—we examined the relationship of age with adherence to ACEi/ARB and BB and time to discontinuation of ACEi/ARB, BB, and MRA after the first presentation of HF. Furthermore, we evaluated the dosing of ACEi/ARB and BB 1 year after the index date compared with the daily target doses of these drugs.

METHODS

The data underlying the analyses of this study are acquired from Statistics Denmark. These data are restricted and their use is only allowed under license and permission for the present study. However, data are available from the author upon reasonable request and with the approval of Statistics Denmark.

Data Sources

This study was conducted as a register-based cohort study of patients with HF in Denmark over the period 2011 to 2018. In Denmark, all citizens are given a unique personal identification number at birth or immigration. The identification number enables linkage of information at an individual level across the nationwide administrative registries described below. These registries allow complete follow-up of all patients, unless they emigrate.

In the present study, data were extracted from 3 registries: (1) The Danish Civil Registration System, which holds information on the personal identification number, emigration/immigration status and date of birth;[7] (2) The Danish National Patient Register, which holds information on diagnoses reported as defined in the *International Classification of Diseases, Tenth Revision* (*ICD-10*) system and dates from all hospital admissions;[8] and (3) The Danish National Prescription Registry, which holds information on all redeemed prescriptions from Danish Pharmacies.[9]

Study Population

We identified all registered Danish citizens aged 18 to 95 years who had a first presentation with HF, defined as a primary diagnosis, from 2011 to 2018 and had both an ACEi/ARB and a BB initiated within 120 days from the date of their HF presentation. Prior studies have shown that patients with HF are accurately identified in Danish registries using *ICD-10* codes.[10] Another recent study has shown that initiation of combined therapy with a BB and either an ACEI or an ARB, over 120 days after first HF presentation, has a high positive predictive value (95%) in identifying patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤40%).[11]

Patients were included if their first presentation with HF was between January 1, 2011 and December 31, 2018. We included patients who received their diagnosis in both an in-hospitalization setting or in a specialized HF outpatient clinic.

Only patients who survived for at least 120 days after their first HF presentation were included in the study. We excluded all patients who emigrated or died within those first 120 days. To ensure all participants had adequate follow-up, we censored individuals who received a first HF diagnosis during the last 120 days of the study period (ie, the last entry date was September 2, 2018).

All patients were categorized into 3 groups according to age at the time of diagnosis: age <65 years; age 65 to 79 years; and 80 years or older. Baseline (index date) was defined as day 120 after first presentation with HF, and the study population comprised those who were still alive and had both an ACEi/ARB, and a BB initiated during the 120 days (Figure S1). An angiotensin receptor neprilysin inhibitors sacubitril/valsartan was not included because very few patients received

this treatment at index (n=65; 0.22%) and after 1 year (n=534; 1.8%).

Drug Dose, Discontinuation, and Adherence

We evaluated the proportion of daily drug dose compared with the target dose at 1 year (365.25 days) after the index date for ACEi/ARB and BB, assuming that 1 year would be enough time to be up-titrated to the maximum tolerated dose. All patients alive and in treatment for at least the first year from baseline were included in this analysis. We only calculated the specific drug that the individual patient initially started on. Time to treatment discontinuation was measured up to 5 years by identifying refilled prescriptions and the number of days each package covered. Discontinuation—the ceasing of pharmacological treatment—was defined as a break of at least 90 days and was based on assumptions of daily doses calculated from dates of refilled prescriptions that included the amount and strength of the ACEi/ARB, BB, and MRA drugs, respectively. Individual drug doses were calculated, and continuation of treatment was assumed if the dose was compatible with at least the minimum daily dose of the specific drug (BB: carvedilol 6.25 mg, bisoprolol 1.25 mg, metoprolol 12.5 mg, nebivolol 1.25 mg, ACEi: enalapril 2.5 mg, captopril 12.5 mg, ramipril 1.25 mg, trandolapril 0.5 mg, lisinopril 2.5 mg, perindopril 2.5 mg, ARB: losartan 12.5 mg, valsartan 80 mg, candesartan 4 mg, MRA: spironolactone 12.5 mg, eplerenone 25 mg). Patients were considered in treatment between the first claimed prescription and 90 days after the estimated duration of the last refilled prescription. A break of 90 days has been shown to indicate a low probability of restarting treatment.[12] Substitution of drugs of the same class (eg, 1 type of BB to another) was not measured and would appear as a continuation of therapy. Since MRA are generally handled differently from ACEi/ARB and BB (start/stop versus dose adjustment), we also analyzed how many patients started MRA again after a break.

Adherence was estimated by the proportion of days covered for ACEi/ARB and BB (ie, the total number of days with the drug available for a patient alive for the whole first year of the follow-up period). Only patients alive for at least the first year from baseline were included in this analysis and contributed equally regardless of discontinuation. We obtained the information of the number of tablets available for the individual patient from refilled prescriptions. This proportion is the number of days the patient has medication supply according to claimed prescriptions, divided by the total number of days in a year (365.25). Thus, proportion of days covered was calculated as coverage from the index day to the end of the first year, day 365.25, which is accepted as an accurate adherence measurement.[13]

Covariates

Comorbidities at baseline were acquired using all in- and outpatient *ICD-10* diagnosis codes up to 5 years before HF diagnosis (Table S1–S2 for diagnoses and corresponding *ICD-10* codes). We defined concomitant pharmacotherapy at baseline as prescriptions filled within the 120 days before the index date for each patient (Table S2 for ATC-codes). Patients with diabetes were identified with refilled prescriptions (ATC-code A10) or *ICD-10* codes (E10-14) for diabetes.

Outcomes

The primary outcomes were the following: (1) the average daily proportion of target drug dose achieved after the first year, (2) adherence to pharmacotherapy during the first year, and (3) the risk of discontinuation of treatment over 5 years. Additional outcomes were the probability of initiating MRA within 5 years of the index date. Supplementary outcomes were hospitalizations for HF, hospitalizations for any cause, all-cause mortality, and the discontinuation of statins as a measure of the patient's overall compliance with a non-HF-related drug. We followed patients from the index date (day 120 after HF diagnosis) until the occurrence of death, emigration, 5-year follow-up, or end of the study (December 31, 2018), whichever happened first.

Statistical Analysis

Throughout, descriptive data for the baseline characteristics were presented as counts and percentages for categorical variables. Medians with the 25th to 75th interquartile range (IQR) were used for reporting continuous variables. The cumulative incidence of discontinuation of ACEi/ARB, BB, or MRA was estimated using the Aalen-Johansen estimator, where the competing risk of death was taken into account. Time to discontinuation of pharmacotherapy after index date was calculated in proportion for each of the 5 following years. We used the cumulative incidence of events for risk of hospitalizations for HF, all-cause hospitalization, and discontinuation of statins, where the competing risk of death also was considered (Aalen-Johansen), and in the risk of all-cause mortality.

Multivariable cause-specific Cox regression was used to evaluate hazard ratios (HR) of the associated risks of treatment discontinuation with a 95% CI. The models were adjusted for age (age group <65, 65–70, and ≥80 years), sex, primary HF diagnosis as in- or outpatient, relevant comorbidities (diabetes, atrial fibrillation, chronic obstructive pulmonary disease, cancer, stroke, history of ischemic heart disease), and

concomitant pharmacotherapy (loop diuretics, MRA, diabetes drugs, thiazides, and statins). Patients in the youngest age group, <65 years of age at their HF presentation, served as the reference group in all the analyses. Relevant interactions between the variables were tested and found insignificant unless otherwise stated.

Subgroup Analysis

To further examine the initiation and discontinuation of appropriate medical therapy in patients with HF, we investigated the cumulative incidence of discontinuation of MRA, if the patients had started MRA therapy together with the baseline criteria of ACEi/ARB+BB in the grace period of 120 days between the first presentation with HF and the index date. Additionally, we evaluated the cumulative incidence of initiating an MRA after a patient's index date. The competing risk of death was also taken into account in these analyses.

Danish Statistics provided access to the national registries. All data management and statistical analysis were performed in SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA) and R (version 4.0.3, R Foundation for Statistical Computing).[14] The level of 2-sided *P* values was considered significant for values <0.05.

Ethics

Register-based studies, where the included individuals cannot be identified, do not require ethical approval, and no informed consent was required. The Danish Data Protection Agency approved access to data for this study (DST project no. 706582, Approval no. P-2019-191).

RESULTS

During the study period of 2011 to 2018, we identified 29 482 individuals in Denmark aged 18 to 95 years with a first HF presentation in Denmark who had both an ACEi/ARB and BB initiated within the first 120 days after diagnosis. A total of 9449 people (33.4%) were <65 years old at presentation, 13 746 (46.6%) were aged between 65 to 79 years, and 6287 (21.3%) were aged 80 years or older. The study cohort is displayed in Figure 1 (study flowchart). Baseline characteristics of the patients in each age group are summarized in Table 1.

Primary Outcomes

Daily Drug Dose (as a Percentage of Target)

The proportions of daily target dose achievements of each drug among patients still receiving the medication at 1 year are listed in Table 2. For BB, people aged

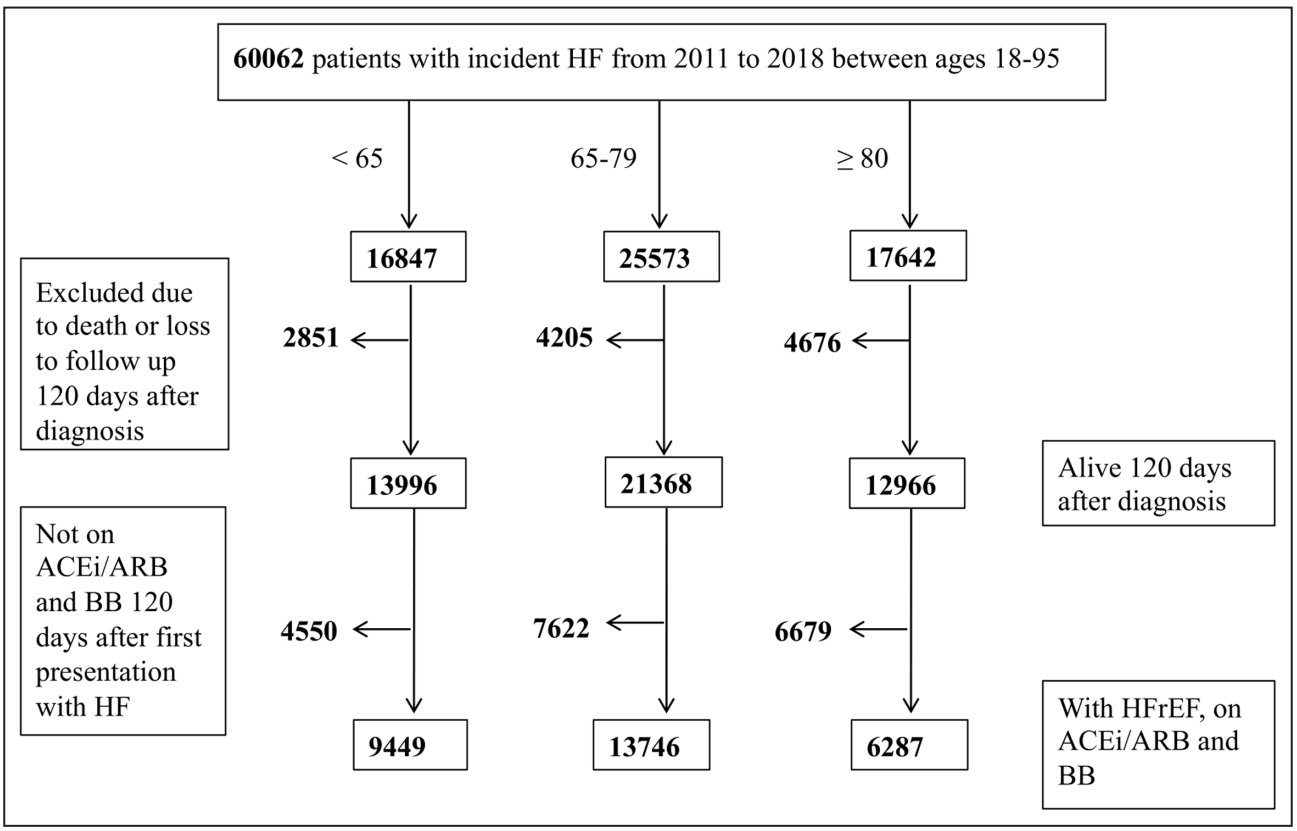

Figure 1. Study flowchart.
ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker; BB, β-blockers; and HF, heart failure.

Table 1. Baseline Characteristics of Survivor Cohort at Day 120 After Inclusion

Demography	Age <65	Age 65–79	Age ≥80	All
Individuals, n (%)	9449 (32)	13 746 (47)	6287 (21)	29 482 (100)
Male, n (%)	7048 (75)	9195 (67)	3377 (54)	19 620 (67)
Age (IQR)	57 (51–62)	73 (69–76)	84 (82–87)	71 (62–79)
Outpatient diagnosis, n (%)	6518 (69)	9261 (67)	3610 (57)	19 389 (66)
Comorbidities, n (%)*				
Diabetes	1811 (19)	3287 (24)	1149 (18)	6247 (21)
AF/AFL	2100 (22)	4922 (36)	2782 (44)	9804 (33)
COPD	676 (7)	1836 (13)	849 (14)	3361 (11)
Cancer	450 (5)	1263 (9)	555 (9)	2268 (8)
IHD	3826 (41)	6021 (45)	2647 (42)	12 674 (43)
Stroke	483 (5)	1116 (8)	547 (9)	2146 (7)
Pharmacotherapy, n (%)†				
β-Blockers	9449 (100)	13 746 (100)	6287 (100)	29 482 (100)
ACEi/ARB	9449 (100)	13 746 (100)	6287 (100)	29 482 (100)
Loop diuretics	5185 (55)	8878 (65)	4937 (79)	19 000 (64)
MRA	4103 (43)	5506 (40)	1928 (31)	11 537 (39)
Antidiabetic drugs	1667 (18)	2926 (21)	968 (15)	5561 (19)
Thiazides	527 (6)	847 (6)	438 (7)	1812 (6)
Statins	5189 (55)	8588 (63)	3084 (49)	16 861 (57)
Antiplatelets	4943 (52)	7546 (55)	3196 (51)	15 685 (53)
Anticoagulants	2753 (29)	5881 (43)	2986 (48)	11 620 (39)
Digoxin	1035 (11)	2325 (17)	1359 (22)	4719 (16)
Ivabradine	157 (2)	126 (1)	27 (0.5)	310 (1)
SGLT2i	35 (0.4)	22 (0.2)	<5 (0.1)	57 (0.2)
Devices, n (%)				
ICD	182 (2)	242 (2)	46 (0.7)	470 (1.6)
CRT	19 (0.2)	51 (0.4)	31 (0.5)	101 (0.3)

Baseline characteristics of the study population at day 120 from inclusion. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker; AF/AFL, atrial fibrillation/atrial flutter; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; outpatient diagnosis, patients diagnosed with presentation HF in an outpatient clinic; and SGLT2i, sodium-glucose co-transporter 2 inhibitors.

*Comorbidities 5 years before inclusion.

†Medication 120 days before inclusion.

<65 years the median dose was 75% (IQR, 38–100) of target dose, for those aged 65 to 79 the median dose was 56% (IQR, 31–100), and for people aged ≥80 years it was 44% (IQR, 25–75) of the target. For ACEi, the corresponding median doses (as a percentage of target) were the following: those <65 years received 100% (IQR, 63–100), 65 to 79 years received 88% (IQR, 50–100), and ≥80 years received 63% (IQR, 38–100). For ARB the corresponding median doses (as a percentage of target) were the following: those <65 years received 75% (IQR, 50–100), 65 to 79 years received 67% (IQR, 38–100), and ≥80 years received 50% (IQR, 33–83).

Cumulative Discontinuation Rate Over 5 Years

The cumulative incidence of discontinuation of ACEi/ARB treatment by 5 years was highest among the most elderly: ≥80 years, (51%), compared with those aged 65 to 79 years (44%) and the youngest age group, <65 years (41%). The cumulative incidence of discontinuation of BB in the oldest age group was 39%, in the age group 65 to 79 years it was 35%, and in the youngest age group <65 years it was 38% (Figure 2A and 2B). After 3 years of follow-up the same tendency was found (Figure S2A and S2B). In a multivariable Cox proportional hazard model adjusted for relevant covariates (Figure S3A and S3B), older age (≥80 years) was associated with a significantly higher rate of discontinuation of treatment of both ACEi/ARB (adjusted HR 1.60 [95% CI, 1.51–1.69]) and BB (adjusted HR 1.33 [95% CI, 1.25–1.41]). The proportional hazards assumptions were checked graphically by Schoenfeld residuals and were found to be valid.

Table 2. Median Target Dose Percentage With IQR at 12 Months After Index Date

Medicine	Percentage of target dose with IQR						Daily target dose
	Aged <65		Aged 65–79		Aged ≥80		
	n	IQR	n	IQR	n	IQR	
BB							
Carvedilol	2756	88 (50–100)	2920	63 (38–100)	911	50 (25–88)	50 mg
Bisoprolol	505	75 (50–100)	887	75 (38–100)	267	50 (38–100)	10 mg
Metoprolol-succinate	3294	63 (31–100)	5364	50 (50–100)	2386	38 (25–63)	200 mg
Nebivolol	116	63 (59–88)	127	63 (50–100)	23	38 (25–100)	10 mg
All BB	6671	75 (38–100)	9298	56 (31–100)	3587	44 (25–75)	
ACEi							
Enalapril	1228	88 (50–100)	1768	88 (50–100)	739	63 (38–100)	20 mg
Captopril	<5	25 (13–50)	10	100 (50–100)	<5	75 (75–75)	100 mg
Ramipril	3229	100 (75–100)	3801	100 (50–100)	1390	63 (38–100)	10 mg
Trandolapril	427	100 (75–100)	592	100 (63–100)	222	88 (50–100)	4 mg
Lisinopril	39	57 (29–64)	50	57 (29–57)	18	54 (36–57)	35 mg
Perindopril	19	100 (100–100)	24	100 (100–100)	14	100 (100–100)	5 mg
All ACEi	4948	100 (63–100)	6245	88 (50–100)	2383	63 (38–100)	
ARB							
Losartan	1595	68 (50–100)	2656	67 (42–92)	950	59 (33–83)	150 mg
Valsartan	6	75 (50–100)	18	57 (50–100)	6	88 (63–100)	320 mg
Candesartan	127	100 (50–100)	176	75 (50–100)	47	50 (25–100)	32 mg
All ARB	1728	75 (50–100)	2850	67 (38–100)	1003	50 (33–83)	

Percentage of achieved dose compared with target dose after 1 year in patients started on the specific drug. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BB, β-blocker; and IQR, interquartile range.

Adherence Over the First Year After Starting Treatment

For ACEi/ARB, those <65 years were adherent 79% of the time during 1 year of follow-up, 65 to 79 years old were adherent 78%, and those ≥80 years were adherent 69% (Figure 3A). The pattern was similar for BB, with those <65 years old adhering to treatment 79% of the time during over a year, those 65 to 79 years old adhering to treatment 79% of the time, and those ≥80 years old adhering to treatment 74% of the time (Figure 3B).

MRA Therapy

The cumulative incidence of discontinuation of MRA in the subgroup started on this treatment within 120 days of presentation with HF was similar in all 3 age groups, ≈50% after 5 years of follow-up (<65, 50%; 65–79, 54%; and ≥80, 56%) (Figure 4A). A total of 4693 stopped MRA treatment or died during follow-up. Thirty-two percent of these patients started MRA again later during follow-up (age <65, 11%; age 65–79, 16%; and age ≥80, 5%). The cumulative incidence of initiating MRA therapy after the index date, in patients who were not started on an MRA at the index date, is shown in Figure 4B. The incidence was the same for the 2 younger age groups (33%). The most elderly, ≥80 years, were 10% less likely to have an MRA initiated after the index date (22%).

Supplementary Analyses: Clinical Outcomes

The risks of hospitalization for HF, hospitalization for any cause, all-cause mortality, and discontinuation of statins according to time after the index date are presented in Figures S4 through S7. There was a graded relationship between advancing age and higher risk of hospitalization for any cause and all-cause mortality. The association between age and hospitalization for HF was less pronounced than for the other events examined. An interaction was found between age group and mortality in patients who had stopped their HF treatment within the first year of follow-up compared with those who stayed on treatment. The interaction was found for discontinuation of both ACEi/ARB and BB. The effect modification by optimal adherence over the first year on mortality was significant in all 3 age groups, but the benefit of prolonged life expectancy was distinctly higher in the youngest age group compared with the elderly. (ACEi/ARB: <65, HR 2.28 [95% CI, 1.87–2.77], P<0.001; 65–79, HR 1.76 [95% CI, 1.58–1.96], P<0.001; ≥80, HR 1.65 [95% CI, 1.48–1.83], P<0.001 [interaction P=0.009]; BB: <65, HR 1.77

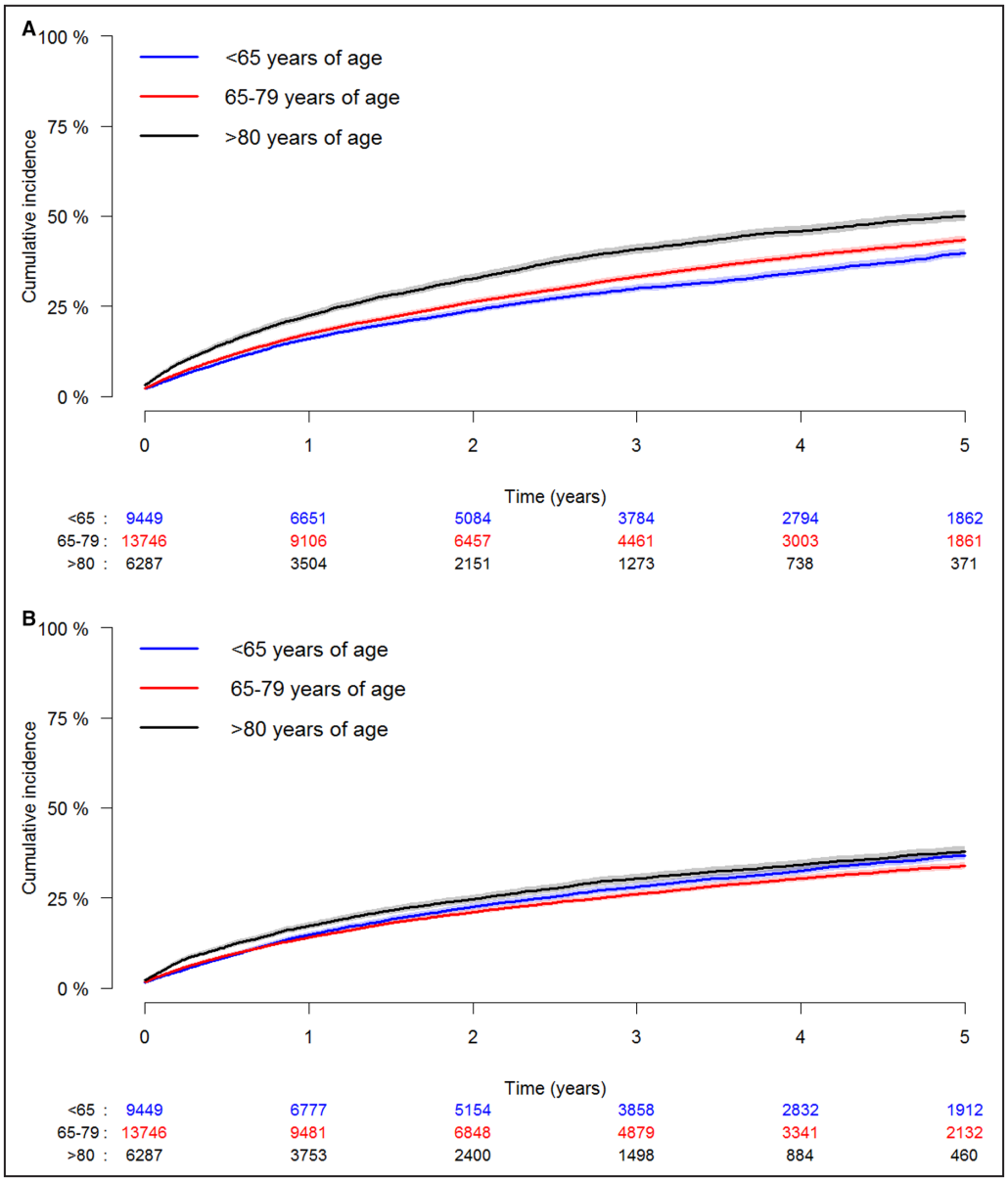

Figure 2. Cumulative incidence of discontinuation of treatment.
A, Discontinuation of ACEi/ARB for ≥90 days. Cumulative incidence curve of discontinuation of ACEi/ARB according to age group for 5 years from index date, accounting for competing risk of death. Bands illustrate 95% CI. The figure is unadjusted for covariates.
ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker. **B**, Discontinuation of β-blockers for ≥90 days. Cumulative incidence curve of discontinuation of β-blockers according to age group for 5 years from index date, accounting for competing risk of death. Bands illustrate 95% CI. The figure is unadjusted for covariates.

[95% CI, 1.43–2.19], *P*<0.001; 65–79, HR 1.22 [95% CI, 1.07–1.38], *P*=0.003; ≥80, HR 1.20 [95% CI, 1.06–1.36], *P*=0.004 [interaction *P*=0.013]). The HR represents the risk of death in those who had stopped their treatment within the first year versus those who were still in treatment. Additionally, the cumulative incidence of discontinuation of statins in patients in statin treatment at index was similar in all 3 age groups: <65, 39%; 65 to 79, 38%; and ≥80, 41%.

DISCUSSION

In this nationwide cohort study of patients with heart failure with reduced ejection fraction in Denmark, the main outcomes investigated were the average proportion of daily target drug dose, and adherence with and time to discontinuation of ACEi/ARB and BB according to age. We found that the oldest patients received lower proportions of daily doses of ACEi/ARB

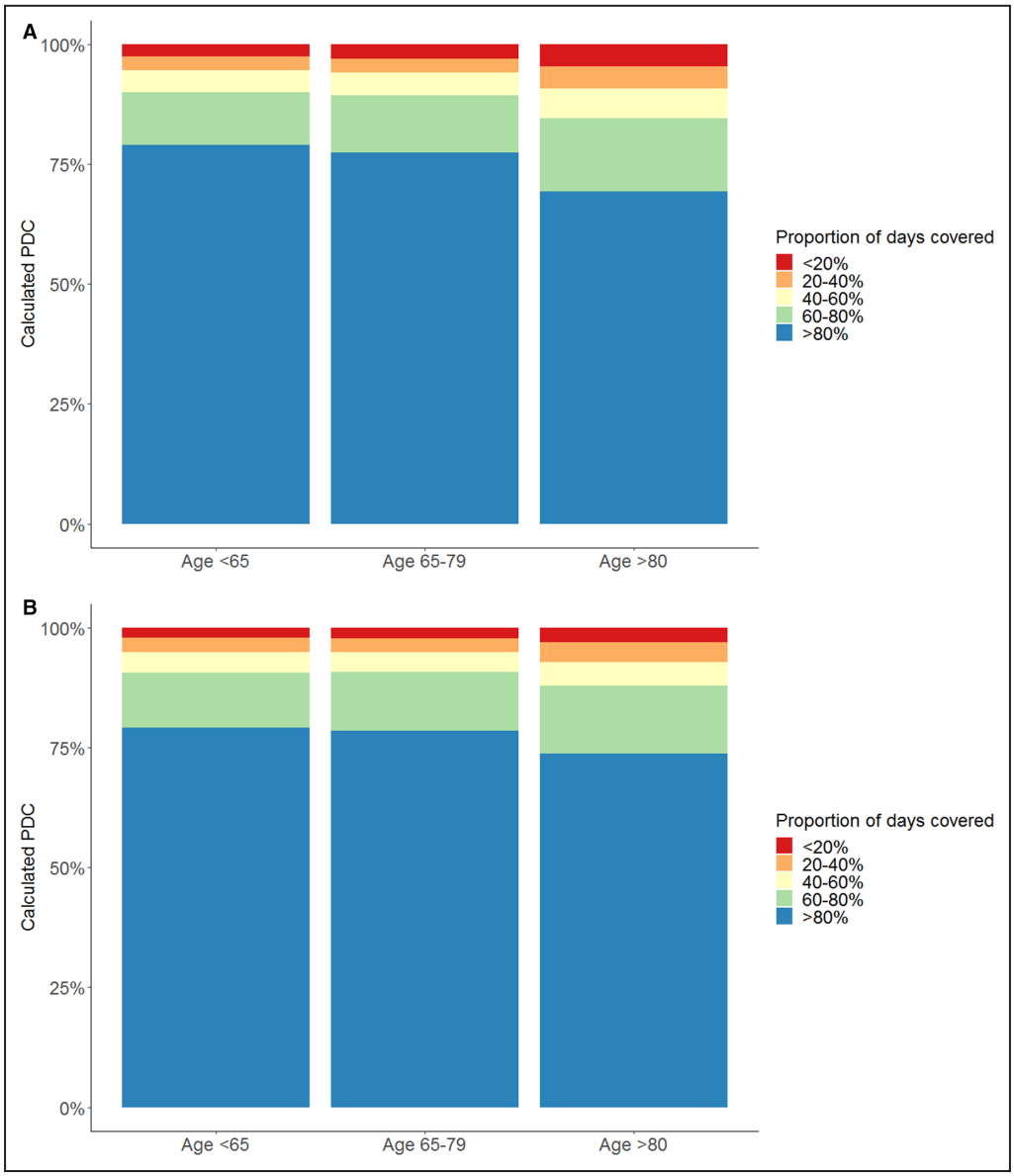

Figure 3. Proportion of days covered.
A, Adherence with ACEi/ARB over the first year. Proportion of days covered (PDC) for ACEi/ARB over the course of a year. PDC >80% of the time for each age group. Under the age of 65 years: 79%, between the age of 65 and 79 years: 78%, 80 years and above 69%. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker. **B**, Adherence with β-blockers over the first year. Proportion of days covered (PDC) for β-blockers over the course of a year. PDC >80% of the time for each age group. Under the age of 65 years: 79%; between the age of 65 and 79 years: 79%; 80 years and above: 74%.

and BB after 1 year and that age ≥80 was associated with higher discontinuation rates and poorer adherence with these drugs. During follow-up, an MRA was less frequently initiated in the most elderly patients, and also the most elderly were less likely to start on MRA again if they had had a break. However, differences in discontinuation and adherence to the drugs investigated were small in absolute numbers between the age groups. We did not observe any differences in the risk of hospitalization for HF by age groups, although all-cause hospitalization and mortality varied by age.

Our findings illustrate that the most elderly are not as likely to continue and adhere to HF treatments and are more likely to stop these than younger patients. Several factors could be related to the discontinuation of therapy. Treatment intolerance, and the decision of the patient's physician, family, or caregiver may be important. In the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity

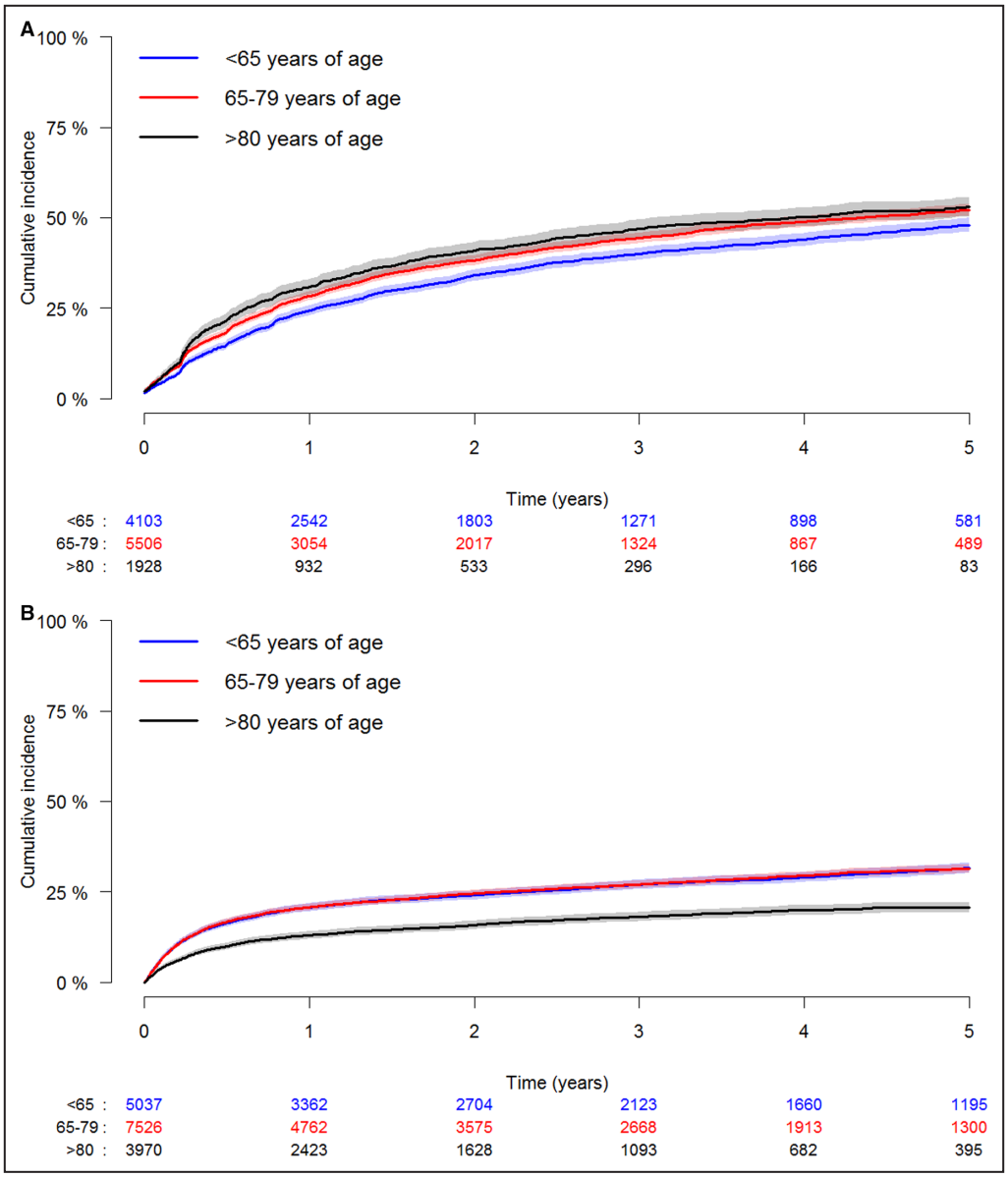

Figure 4. Cumulative incidence of outcomes for MRA treatment.
A, Discontinuation of MRA for ≥90 days. Cumulative incidence curve of discontinuation of MRA according to age group for 5 years from index date, accounting for competing risk for discontinuation because of risk of death. Bands illustrate 95% CI. The figure is unadjusted for covariates. **B**, Initiation of MRA after 120 days. Cumulative incidence curve of the probability of MRA initiation after index date according to age group for 5 years from index date, accounting for competing risk of death. Bands illustrate 95% CI. The figure is unadjusted for covariates. MRA indicates mineralocorticoid receptor antagonist.

(CHARM) program, where the study population had a mean age of 66 years (9.1% ≥80), the mean daily dose received of the ARB study drug candesartan was 24 mg (75% of target dose), and 92% of the study population were at least 80% adherent over a median time of 38 months.[15,16] Patients ≥80 years received a slightly lower mean dose of candesartan than the overall study group, 22.3 mg (70% of target dose).[15] Comparing this to our results (ACEi, <65 years received a mean of 100% of target dose; 65–70, 88%; and ≥80, 63%; ARB: <65, 75%; 65–79, 67%; ≥80, 50%), the most elderly received a much lower proportion of daily target dose than both the younger patients in our study cohort and most elderly ≥80 in CHARM. However, the patients in CHARM were carefully selected and had to meet specific entry criteria, excluding patients with symptomatic hypotension, hyperkalemia, and poor kidney function, among other reasons.[15] In a smaller Dutch cohort study by Veenis et al, increasing age was associated with lower drug doses for both ACEi/

ARB and BB compared with younger patients, which our findings support.[17] Similar results were seen in a study by Stolfo et al that found a direct relationship between age and target dose achievement.[18] These findings further reveal the gulf between clinical trials and epidemiological research. There is a need to design future clinical trials to incorporate patients more representative of the general population to better understand the issues we face in real-life practice and hopefully improve outcomes in all patients with HF. Our large and contemporary study of elderly patients in Denmark suggests that there are other unreported factors influencing dosing and adherence in the "real world" compared with a trial cohort. Our finding of a mean adherence to an ACEi/ARB of 69.4% to 79.2%, depending on age, seems to reflect reasonable measure given that the patients in CHARM were carefully selected. However, our patients were also selected because they had to survive the first 120 days after presentation and be treated with both an ACEi/ARB and a BB. In this way, we may have excluded the most elderly and ill patients; however, we still enrolled a much higher proportion of patients ≥80 years than in CHARM (21.3% versus 9.1%). The lower risk of discontinuation and greater adherence with BBs than ACEi/ARB in older patients are notable. This finding is also consistent with the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) trial, which was a dedicated study with the BB nebivolol in patients ≥70 years of age (median age 75 [69–95]).[19] Nebivolol was well tolerated in SENIORS, in keeping with subgroup findings from other placebo-controlled BB trials and the Cardiac Insufficency Bisoprolol Study in Elderly (CIBIS-ELD) trial (however, slower up-titration with advancing age).[20]

The reasons for the difference between ACEi/ARB and BB tolerability in the elderly are uncertain. It might reflect kidney function, which declines with age and may preclude continuation of ACEi/ARB but should not affect BB use. Similarly, in our statin "control" analysis, there was no significant difference between the age groups, which might also suggest kidney function was the major determinant of ACEi/ARB discontinuation. However, MRA use is also influenced by kidney function and yet the difference in time to discontinuation between younger and older patients was not as pronounced for these drugs, although patients receiving an MRA may have been highly selected. We found that patients of all ages had similar discontinuation patterns with MRA therapy in a 5-year follow-up period. However, we also observed that the most elderly are much less likely to be started on an MRA than younger patients. However, when started, they appear to stay on therapy, suggesting that those selected for this treatment do tolerate it. Whether the low rate of prescription of MRAs legitimately reflects factors such as poor kidney function, risk of hyperkalemia, and hypotension in patients in whom the 2 first-choice HF drugs are only tolerated in lower doses, concerns about polypharmacy, inertia, or even nihilism in the most elderly cannot be discerned from our data.

Our supplementary analysis of outcomes observed that most elderly patients had the highest mortality risk, probably explained by age.[15] Although there was an association between adherence and mortality in all age groups, this was strongest in the youngest patients and weaker in older individuals. We cannot deduce from our observational data whether this observation reflects a greater effect of therapy on mortality in younger compared with older patients or that younger patients are sicker when they have therapies withdrawn, or a combination of these or some other reason. Additionally, we found no relationship between age and the risk of hospitalization for HF. The incidence of HF hospitalization may be explained by adequate treatment despite the observed differences in adherence to the recommended pharmacotherapies. Still, patients aged ≥80 years had a higher risk of all-cause hospitalization. Whether this reflects a hospitalization for comorbidities or HF can be difficult to separate since many elderly patients may have admissions for more than 1 reason (eg, the combination of pneumonia and HF in combination).

Limitations

In this study of real-life data, our key strength is the completeness of the Danish registries and access to complete follow-up of our large study population. However, the study has some limitations that should be acknowledged. The definition of HF with reduced ejection fraction is based on the study of Madelaire et al.[11] Detailed data on left ejection fraction from echocardiograms were not available. A further fundamental limitation is the lack of knowledge of potential causes of treatment intolerance such as kidney function, and blood pressure. These along with functional class and use of device therapies also represent potentially unmeasured confounders. An important influence of these factors on outcome cannot be discounted. Therefore, we may have overestimated the strength of the association between age and discontinuation in the Cox proportional hazard model. However, in clinical practice, it does not change the outcome that elderly patients—often coexisting with poor kidney function and a poor functional class—have a slightly lower adherence and higher discontinuation of recommended pharmacotherapies. Estimating discontinuation and adherence based on data of prescriptions refills could overestimate the actual consumption and continuity of treatment. The measure is highly dependent on a patient's adherence to their prescribed treatment plan. Furthermore,

the reasons for nonadherence and discontinuation of treatment remain unknown. However, assessing prescription refills as a measure for adherence is an accepted method in population-based studies.[21]

CONCLUSIONS

This nationwide study of a consecutive cohort of patients with heart failure with reduced ejection fraction showed that advanced age was associated with lower proportions of daily target doses, lower adherence and a higher rate of discontinuation of 2 key evidence-based pharmacotherapies (ACEi/ARB and BBs), and patients ≥80 years had the highest risks of death and hospital admissions. These findings suggest that the most elderly patients should be the targets of early initiatives to improve adherence and reduce discontinuation of appropriate HF therapies.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figures S1–S7

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Supplemental Material

Table S1: Comorbidity diagnosis and corresponding ICD-10 codes

Comorbidity	**ICD-10 codes**	
Heart failure	I42, I50, I110, J81	
Ischemic Heart Disease	I20-I25	
Stroke	I63-64, I74, G458-459	
Atrial fibrillation/flutter	I48	
Diabetes	E10-14	Diabetes as a comorbidity was defined by the corresponding ICD-10 codes or ATC classification codes for antidiabetic drugs.
Cancer	C0-C9	
Chronic Obstructive Pulmonary Disease	J4	

Table S1: ICD, International Classification of Diseases.

Table S2: ATC classification codes

Pharmacotherapy	**ATC codes**
Beta-blockers (BB)	C07AB02, C07AB12, C07AB07, C07AG02
Angiotensin-renin system blockers (ACEi and ARB)	C09AA01-05, C09AA10, C09CA01, C09CA03, C09CA06
Mineralocorticoid receptor antagonist	C03DA
Statins	C10A
Antidiabetes drugs	A10
Loop-diuretics	C03C
Thiazides	C03A
Antiplatelets	B01AC04, B01AC06-07, B01AC22, B01AC24,
Anticoagulants	B01AE, B01AF, B01AA0
Digoxin	C01AA05
Ivabradine	C01EB17
Sodium-glucose cotransporter-2 inhibitors (SGLT2i)	A10BK01, A10BK03
Angiotensin Receptor-Neprilysin Inhibitor (ARNI)	C09DX04

Table S2: ATC, Anatomical Therapeutic Chemical.

Figure S1: Study design

Figure S1. HF, heart failure; ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers; BB, beta-blockers.

Figure S2a: Cumulative incidence of discontinuation of ACEi/ARB after 3 years

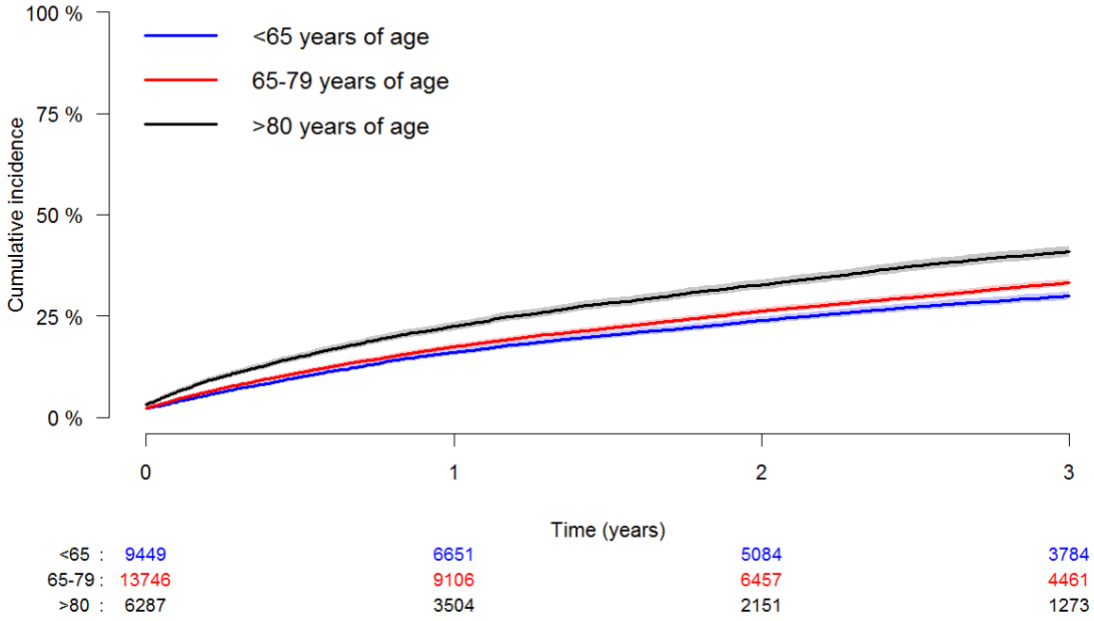

Figure S2a. ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers. Cumulative incidence curve of discontinuation of ACEi/ARB according to age group for 3 years from index date, accounting for competing risk of death. Bands illustrate 95% confidence interval. The figure is unadjusted for covariates.

Figure S2b: Cumulative incidence of discontinuation Beta-blockers after 3 years

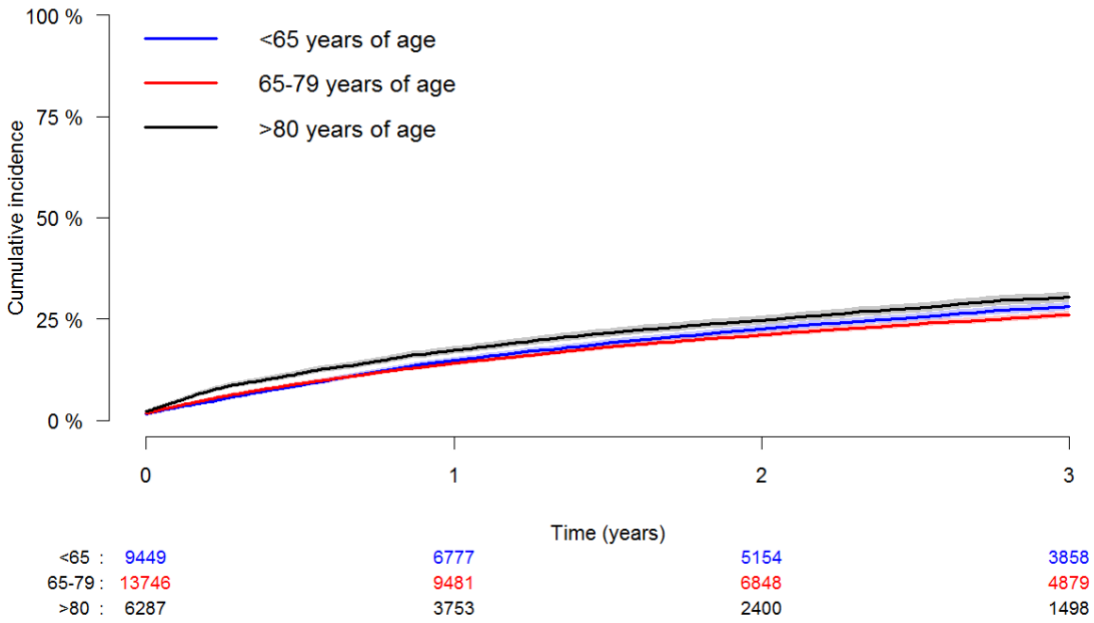

Figure S2b. Cumulative incidence curve of discontinuation of beta-blockers according to age group for 3 years from index date, accounting for competing risk of death. Bands illustrate 95% confidence interval. The figure is unadjusted for covariates.

Figure S3a: Covariates associated with discontinuation of ACEi/ARB

Variable		N	Hazard ratio	p
Age group	<65 years of age	9449	Reference	
	65-79 years of age	13746	1.11 (1.05, 1.17)	<0.001
	>80 years of age	6287	1.52 (1.43, 1.62)	<0.001
Male sex		29482	0.92 (0.88, 0.96)	<0.001
Outpatient		29482	0.89 (0.85, 0.94)	<0.001
Diabetes		29482	1.26 (1.16, 1.37)	<0.001
Atrial fibrillation		29482	1.06 (1.02, 1.11)	0.009
COPD		29482	1.15 (1.07, 1.22)	<0.001
Cancer		29482	1.31 (1.22, 1.41)	<0.001
Stroke		29482	1.07 (0.99, 1.16)	0.093
IHD		29482	1.10 (1.05, 1.16)	<0.001
Loop diuretics		29482	1.19 (1.13, 1.25)	<0.001
MRA		29482	0.96 (0.91, 1.00)	0.047
Antidiabetic drugs		29482	1.10 (1.02, 1.18)	0.018
Thiazids		29482	1.03 (0.95, 1.13)	0.477
Statins		29482	0.86 (0.82, 0.91)	<0.001

Figure S3a. ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers. HF, heart failure; Out patient diagnosis, patients diagnosed with presentation HF in an out patient clinic. COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist

Figure S3b: Covariates associated with discontinuation of Beta-blockers

Variable		N	Hazard ratio	p
Age group	<65 years of age	9449	Reference	
	65-79 years of age	13746	1.11 (1.05, 1.17)	<0.001
	>80 years of age	6287	1.52 (1.43, 1.62)	<0.001
Male sex		29482	0.92 (0.88, 0.96)	<0.001
Outpatient		29482	0.89 (0.85, 0.94)	<0.001
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Statins		29482	0.86 (0.82, 0.91)	<0.001

Figure S3b. HF, heart failure; Out patient diagnosis, patients diagnosed with presentation HF in an out patient clinic. COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist

Figure S4: Cumulative incidence of HF hospitalizations after index date

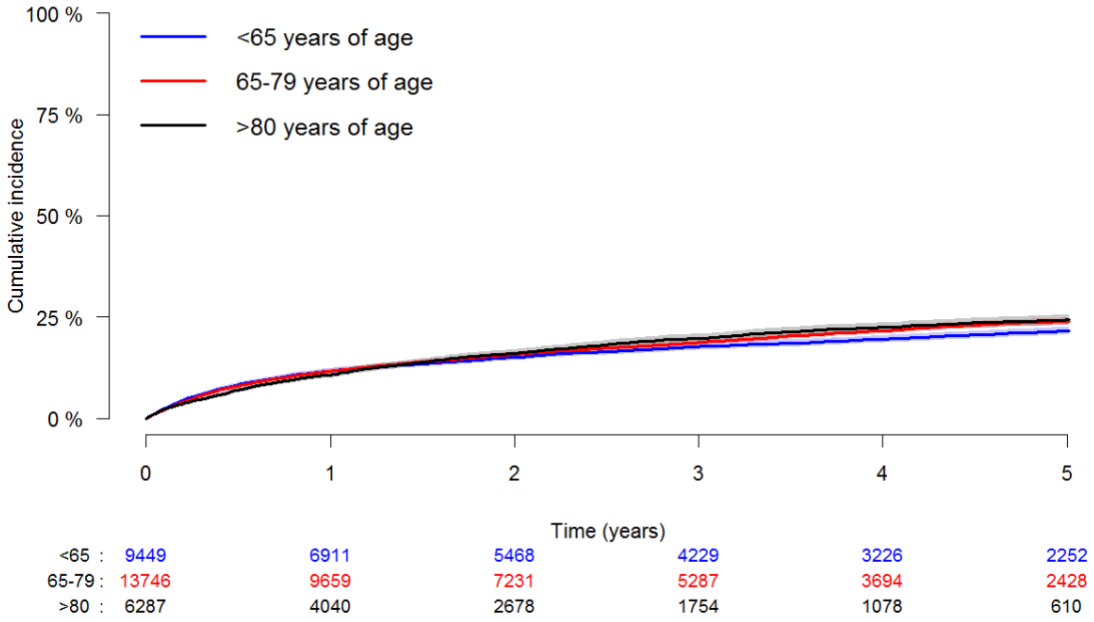

Figure S4. Cumulative incidence curve of heart failure hospitalizations according to age group for 5 years from index date, accounting for competing risk of death. Bands illustrate 95% confidence interval. The figure is unadjusted for covariates. HF, heart failure.

Figure S5: Cumulative incidence of all-cause hospitalization after index date

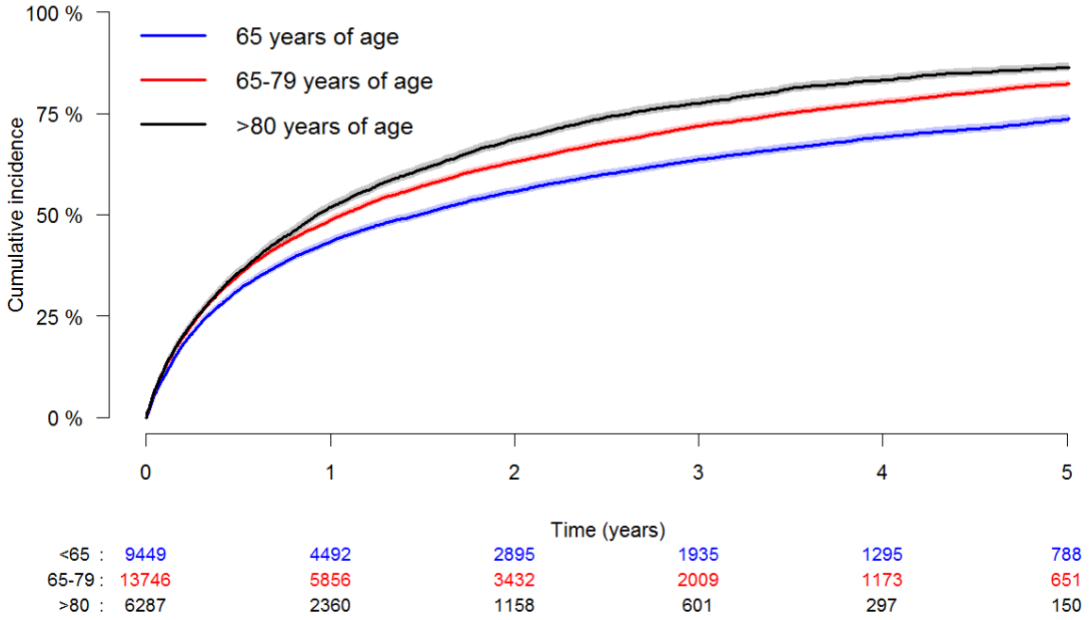

Figure S5. Cumulative incidence curve of all-cause hospitalizations according to age group for 5 years from index date, accounting for competing risk of death. Bands illustrate 95% confidence interval. The figure is unadjusted for covariates.

Figure S6: Cumulative incidence of all-cause mortality after index date

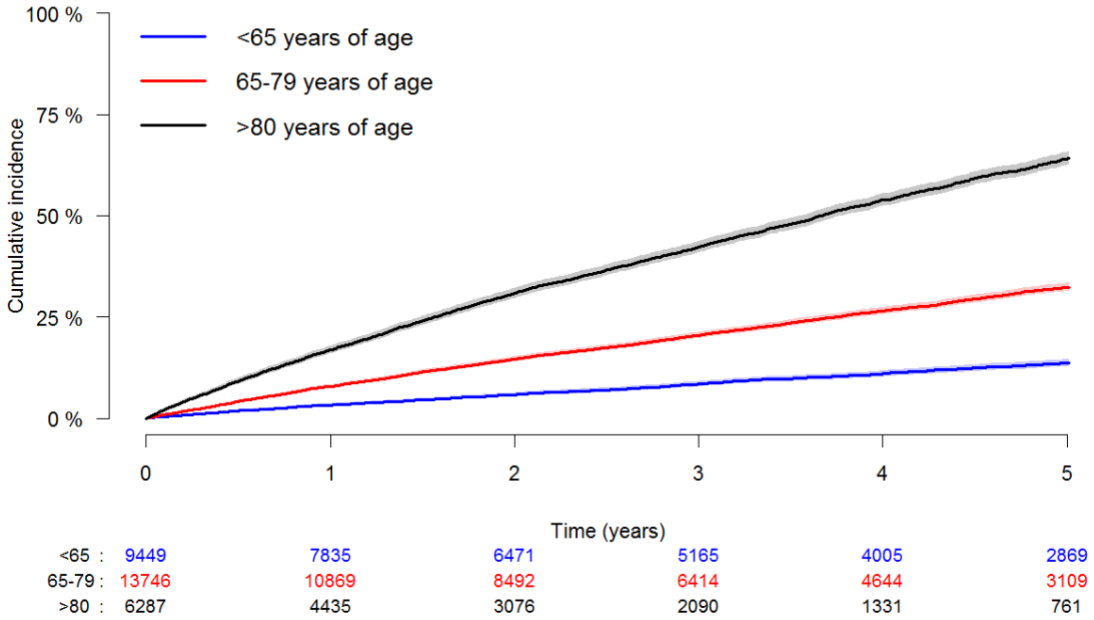

Figure S6. Cumulative incidence curve of discontinuation all-cause mortality according to age group for 5 years from index date. Bands illustrate 95% confidence interval. The figure is unadjusted for covariates.

Figure S7: Cumulative incidence of discontinuation of statins

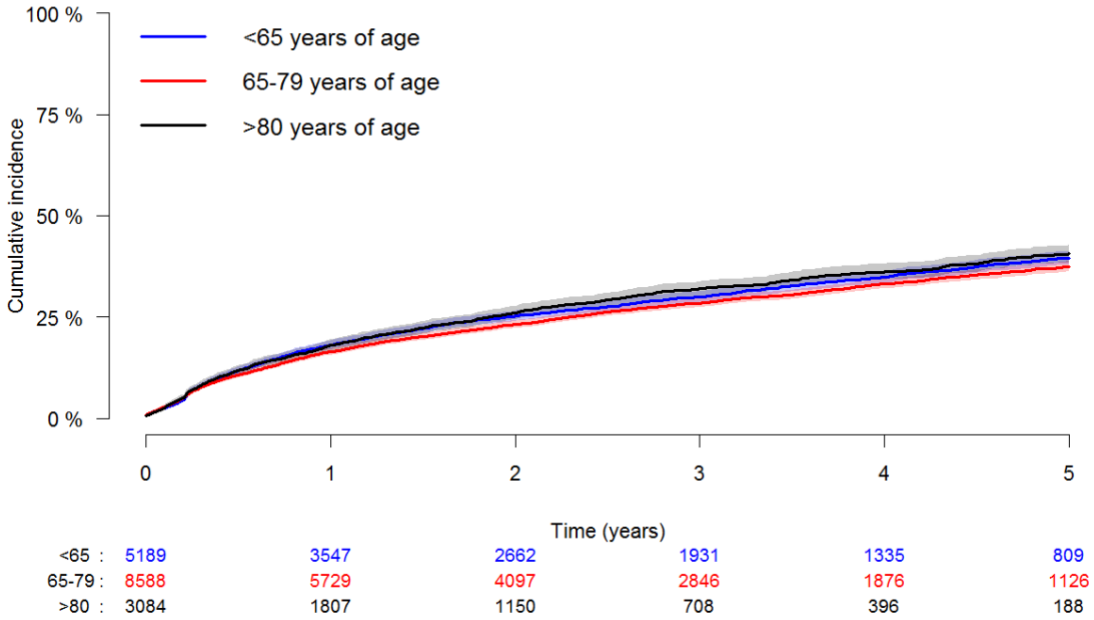

Figure S7. Cumulative incidence curve of discontinuation of statins according to age group for 5 years from index date, accounting for competing risk of death. Bands illustrate 95% confidence interval. The figure is unadjusted for covariates.