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Antidepressant use and risk for mortality in 121,252 heart failure patients with or without a diagnosis of clinical depression

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ABSTRACT

Background: Depression is a risk factor for mortality in patients with heart failure (HF), however, treating depression with antidepressant therapy does not seem to improve survival. We examined the prevalence of antidepressant use in HF patients, the correlates of antidepressant use subsequent to hospital discharge and the relation between antidepressant use, clinical depression and mortality in patients with HF.
Methods: 121,252 HF patients surviving first hospitalization were stratified by antidepressant use and a diagnosis of clinical depression.
Results: In total, 15.6% (19,348) received antidepressants at baseline, of which 86.7% (16,780) had no diagnosis of clinical depression. Female gender, older age, higher socio-economic status, more comorbidities, increased use of statins, spironolactone and aspirin, lower use of beta-blockers and ACE-inhibitors, greater HF severity and a diagnosis of clinical depression were independently associated with antidepressant use. Patients using no antidepressants with clinical depression and patients using antidepressants, with or without clinical depression, had a significantly higher risk for all-cause mortality (HR, 1.25; 95% CI, 1.15–1.36; HR, 1.24; 95% CI, 1.22–1.27; HR, 1.21; 95% CI, 1.16–1.27, respectively) and CV-mortality (HR: 1.17; 95% CI, 1.14–1.20, $P < .001$; HR: 1.20; 95% CI, 1.08–1.34, $P < .001$; HR: 1.21; 95% CI, 1.12–1.29, $P < .001$, respectively) as compared to patients not using antidepressants without depression in adjusted analysis.
Conclusion: Patients with HF taking antidepressants had an increased risk for all-cause and CV-mortality, irrespectively of having clinical depression. These results highlight the importance of further examining the antidepressant prescription pattern in patients with HF, as this may be crucial in understanding the antidepressant effects on cardiac function and mortality.

1. Introduction

Depression is prevalent in 15%–40% of patients with heart failure (HF) and increases the risk for mortality and re-hospitalization [1,2]. Given the assumption that treating depression in HF would improve prognosis, there has been a considerable rise in antidepressant use in these patients over the past years [1,3,4]. Paradoxically, effectively treating depression with antidepressant therapy does not seem to be a guarantee for successfully reducing the risk for adverse events in patients with cardiovascular disease [5,6], with some studies even suggesting an increased risk for HF mortality [3,7]. The association between antidepressant use and cardiovascular events appears to depend on the class of antidepressant medication [8], and may vary across different cardiovascular populations, definitions of antidepressant use and statistical analyses used [1]. Not all studies adjusted statistically for depressive symptoms, nor examined the combined effect of antidepressant use and depressive symptoms [9–12], let alone included a diagnosis of clinical depression.

The two main classes of antidepressant medication are the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs) [1]. TCAs are known to have pharmacological properties that can precipitate life-threatening arrhythmias, increase heart rate and orthostatic hypotension and prolong QT-interval in patients with ischemic heart disease [13]. Despite these side effects only a few studies found that

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TCAs significantly increased the risk for cardiovascular disease [8], ischemic heart disease [10] and myocardial infarction [9] in population-based samples, or mortality in patients with pre-existing HF [3].

Findings on SSRIs suggest that their use in cardiac patients is relatively safe and induces only minimal cardiovascular effects, making them preferable over TCAs [13]. Two studies confirmed the safety of SSRIs by showing reduced incidence of myocardial infarction or mortality in HF patients using SSRIs [14,15]. However, other studies found no significant difference in risk in relation to SSRI use [5,8–12].

Given these gaps in our knowledge, there is an urgent need to re-examine the prescription pattern of antidepressants post HF diagnosis and the mortality risk associated with antidepressant use in large cohorts of HF patients in order to optimize the treatment and care for these patients. Hence, the objectives of the current study were to (1) examine the prevalence of antidepressant use in HF patients 5-years post diagnosis, (2) identify the correlates of antidepressant use subsequent to hospital discharge, and (3) examine the relation between antidepressant use and both all-cause and cardiovascular (CV) mortality in a large sample of HF patients. Information on HF diagnosis, use and type of antidepressant, and clinical diagnosis of depression was derived from the Danish registries. These registries provide a unique opportunity to track antidepressant use over time and to examine whether the association between antidepressant use and mortality is similar in HF patients with and without a clinical diagnosis of depression, while controlling for potential confounders.

2. Methods

2.1. Data sources and study population

The Danish National Health Service provides tax-supported health care, which allows access to general practitioners and hospitals, and partially reimburses prescribed drugs. Using the civil registry number, which is unique to every Danish citizen, it is possible to perform a complete linkage of all administrative population-based registries at the individual level. The Danish registries include data on socio-demographic characteristics, socio-economic status, hospitalizations, vital status, and prescribed medications. Vital status was obtained from the Danish Civil Registration System. Diagnostic information from hospital admissions are coded using the International Classification of Diseases, Tenth Revision (ICD-10), and drugs were grouped according to Anatomical Therapeutic Chemical (ATC) codes.

2.2. Study population

For this study, we obtained information from all individuals who survived their first hospital admission for HF between 1997 and 2010 (ICD-codes: I11.0, I50, I42, and J81). First time admission was defined as no previous admission for HF since 1978. The registry did not allow us to distinguish between HF with preserved or reduced ejection fraction. A diagnosis of clinical depression included unipolar depression (i.e., major depressive episode, dysthymia) (ICD-codes: DF32-DF39). The prevalence of clinical depression was extracted from the registry at 90 days after discharge and at 1- and 5-year follow-up. To ensure equal time for all patients to claim prescriptions for new medications after hospitalization, we only included patients alive 90 days after discharge. This approach has been used in previous Danish studies that have included information on medication prescriptions [3]. The observational time started 90 days after discharge (from now on referred to as 'study baseline') and followed patients at risk for all-cause and CV mortality until December 31st 2010.

2.3. Medical treatment: Cardiac and antidepressant medication

We used the following ATC codes to identify the use of antidepressants (N06A), beta-blockers (C07), statins (C10A), loop diuretics (C03C), spironolactone (C03D), aspirin (B01AC06) and angiotensin-converting enzyme (ACE) inhibitors (C09). The use of antidepressant and cardiac medications was defined as at least 1 claimed prescription within 90 days after discharge. The use of antidepressants was also examined at 1- and 5-year follow-up.

2.4. Statistical analysis

All continuous variables were tested for normal distribution. Continuous and categorical variables were described by the presence or absence of clinical depression and/or the use of antidepressant medication. Statistical comparisons were made between groups using Pearson's Chi-square test for categorical variables and analysis of variance for continuous variables. Multivariable logistic regression was used to examine the correlates of antidepressant use, thereby including age, gender, socio-economic status, days of hospitalization, comorbidity (Charlson's Comorbidity Index version 9.5.12), HF severity, other cardiac medications (i.e., beta-blockers, statins, ACE-inhibitors), and clinical diagnosis of depression. To determine the severity of HF, the average daily dosage of loop diuretics in the first 90 days after discharge was calculated (group I: 0–39 mg; group II: 40–80 mg; group III: 81–160 mg; group IV: >160 mg) [3]. Socio-economic status was calculated using the family income 5 years before the first diagnosis of HF, divided by the number of family members. All incomes were then divided into quintiles to generate equal size income groups.

Kaplan–Meier plots and multivariable Cox proportional hazard regression analysis were used to compare all-cause and CV mortality stratified by antidepressant use and clinical diagnosis of depression for the following 4 groups: (1) patients using no antidepressants with no clinical diagnosis of depression, (2) patients using no antidepressants with a clinical diagnosis of depression, (3) patients using antidepressants with no clinical diagnosis of depression, and (3) patients using antidepressants with a clinical diagnosis of depression. Multivariable models were fitted with socio-demographic (age, gender, marital status), socio-economic and clinical variables (days of hospitalization, comorbidity, HF severity, cardiac medication). Another Cox proportional hazard regression analysis was performed examining the impact of the use of different antidepressant groups (i.e., TCAs, SSRI, other (tetra, NaSSA, SNRI)) as compared to no antidepressant use, and on the impact of different types of antidepressants on all-cause and CV mortality. All analyses were performed using the Stata statistical package version 11.2 (Stata Corp, College Station, Tex).

2.5. Ethics

The Danish Data Protection Agency approved the study (No. 2003–54-1269). In Denmark, historical cohort studies based on data from administrative registers do not require further ethics approval.

3. Results

3.1. Baseline characteristics

A total of 121,252 patients survived their first hospitalization for HF during the study period. Baseline characteristics of patients in the total sample and stratified by antidepressant use at baseline (90 days after discharge) are shown in Table 1. Of all patients, 84.4% (101,904) received no antidepressants, of which 99.2% (101,095) had no clinical depression, while 0.8% (809) had clinical depression. The remaining 15.6% (19,348) received antidepressants, of which 13.3% (2568) had a diagnosis of clinical depression, while 86.7% (16,780) of the patients did not.

At 1-year, 98,590 patients were still alive, with 22.6% (22,281) receiving antidepressant treatment while only 2.0% (1972) of these patients also had a diagnosis of clinical depression. At 5 years, 37,813 patients were still alive, of which 32.0% (12,100) received antidepressant treatment, while only 1% (378) of these patients also had a diagnosis of clinical depression.

3.2. Correlates of antidepressant use

In the multivariable logistic regression analysis, female gender, older age, higher socio-economic status, more comorbidities, increased use of statin, spironolactone and aspirin, lower use of beta-blockers and ACE-inhibitors, greater HF severity and a diagnosis of clinical depression were independently associated with antidepressant use subsequent to discharge (Table 2).

3.3. Incidence of all-cause and CV mortality during the follow-up period

The median follow-up duration was 2.9 years (interquartile range 1.1–5.6 years). During this period, 61.1% (61,800) of the patients died due to all-cause mortality in the group of no antidepressants and no clinical depression, 68.2% (552) of the patients died in the group no antidepressants with clinical depression, 70.3% (11,801) died in the group using antidepressants without clinical depression, and 71.3% (21,830) patients died in the group using antidepressants with clinical depression ($P < .001$). The 1-, 3- and 5-year crude all-cause mortality rates were 19.0%, 49.3% and 69.8%.

Table 1
Baseline characteristics for the total sample and stratified according to antidepressant use at baseline (90 days after discharge).

	Total sample n = 121,252	No antidepressant use n = 101,904		Antidepressant use n = 19,348		P-value
		No depression	*Depression*	*No depression*	*Depression*	
		n = 101,095	n = 809	n = 16,780	n = 2568	
Age (mean, SD)	73.5 ± 13.6	73.0 ± 14.6	74.8 ± 11.5	74.0 ± 12.3	77.3 ± 10.8	<.001
Sex, males	64,342 (53.3%)	56,502 (55.9%)	320 (39.6%)	6950 (41.4%)	1210 (35.8%)	<.001
Socio-economic status						<.001
0	22,683 (18.7%)	19,172 (19.1%)	114 (14.1%)	3002 (17.9%)	392 (15.3%)	
1	23,144 (19.1%)	18,847 (18.6%)	176 (21.6%)	3525 (21.0%)	606 (23.6%)	
2	23,806 (19.5%)	19,166 (18.9%)	193 (23.9%)	3793 (22.6%)	652 (25.4%)	
3	24,746 (20.4%)	20,452 (20.3%)	190 (23.5%)	3557 (21.2%)	548 (21.3%)	
4	26,873 (22.3%)	23,458 (23.3%)	136 (16.9%)	2903 (17.3%)	370 (14.4%)	
HF Severity group[a]						<.001
I	45,492 (37.5%)	38,694 (38.3%)	333 (41.2%)	5558 (33.1%)	916 (35.3%)	
II	31,424 (25.9%)	26,778 (26.5%)	175 (31.8%)	3931 (23.4%)	513 (21.0%)	
III	22,724 (18.7%)	18,460 (18.3%)	146 (39.2%)	3576 (21.3%)	551 (21.1%)	
IV	21,612 (17.8%)	17,163 (17.0%)	155 (17.9%)	3715 (22.1%)	588 (22.6%)	
Medication after discharge						
Beta-blockers	51,094 (42.1%)	43,864 (43.4%)	257 (31.8%)	6206 (37.0%)	767 (29.9%)	<.001
Statins	28,707 (23.7%)	24,238 (24.0%)	132 (16.4%)	3799 (22.6%)	538 (21.0%)	<.001
ACE-inhibitors	63,910 (52.7%)	54,578 (54.0%)	317 (39.2%)	7981 (47.5%)	1034 (40.3%)	<.001
Spironolactone	26,514 (21.9%)	22,080 (21.8%)	145 (17.9%)	3799 (22.6%)	490 (19.1%)	<.001
Aspirin	55,183 (45.5%)	45,686 (45.2%)	293 (36.2%)	8000 (47.7%)	1204 (46.9%)	<.001
Comorbidity and history						
Myocardial infarction	30,671 (25.3%)	25,887 (25.4%)	217 (26.8%)	4155 (24.8%)	611 (23.8%)	.063
Ischemic heart disease	39,941 (32.9%)	33,695 (33.0%)	251 (31.0%)	5541 (33.0%)	806 (31.4%)	.233
Comorbidity Index						
0	57,083 (47.1%)	49,246 (49.7%)	194 (24.0%)	5974 (35.6%)	669 (26.1%)	<.001
1	30,544 (25.2%)	24,753 (24.5%)	223 (27.6%)	4784 (28.5%)	784 (30.5%)	
2	13,789 (11.4%)	10,820 (10.7%)	138 (17.1%)	2393 (14.3%)	438 (17.1%)	
3	9319 (7.7%)	7425 (7.3%)	105 (13.0%)	1531 (9.1%)	258 (10.1%)	
4	5217 (4.3%)	3891 (3.9%)	80 (9.9%)	1034 (6.2%)	212 (8.3%)	
≥5	5300 (4.4%)	4960 (3.9%)	69 (8.5%)	1064 (6.3%)	207 (8.1%)	
Hospitalization (days, mean, SD)	46.0 ± 85.5	38.0 ± 73.0	49.8 ± 85.5	57.5 ± 100.1	41.4 ± 76.3	<.001

Data are represented as mean ± SD or n (%).
[a] According to average daily dosage of loop diuretic (furosemide) in the first 90 days after discharge (group 1, 0–39 mg; group 2, 40–80 mg; group 3, 81–160 mg; group 4, >160 mg).

3.4. Clinical depression, antidepressant use, all-cause and CV mortality

Univariable Cox proportional hazard regression analysis showed that patients using no antidepressants with clinical depression (HR: 1.55; 95% CI, 1.42–1.68, P < .001), patients using antidepressants without clinical depression (HR: 1.45; 95% CI, 1.43–1.48, P < .001), and patients using antidepressants with clinical depression (HR: 1.68; 95% CI, 1.60–1.76, P < .001) had a greater risk of all-cause mortality in comparison to HF patients not using antidepressants and having no clinical depression (Fig. 1). Also in multivariable Cox proportional hazard analyses, patients not using antidepressants with clinical depression and patients using antidepressants, with or without clinical depression, had a significantly higher risk for all-cause mortality (Ps < .001) compared to patients not using antidepressants without clinical depression (Table 3) Also in relation to CV-mortality, the univariable Cox proportional hazard analyses showed that patients using no antidepressants with clinical depression (HR: 1.23; 95% CI, 1.20–1.26, P < .001), patients using antidepressants without clinical depression (HR: 1.27; 95% CI, 1.40–1.42, P < .001), and patients using antidepressants with clinical depression (HR: 1.33; 95% CI, 1.26–1.42, P < .001) had a greater risk of mortality in comparison to HF patients not using antidepressants and having no clinical depression. These results remained significant in the multivariable Cox proportional hazard analyses (Ps < .001). When excluding the group of patients not using antidepressants without clinical depression, there was no longer a significant difference in all-cause or CV-mortality between the remaining groups (Ps > .27).

Table 2
Associates of antidepressant use at baseline (90 days after discharge) in order of relative importance[b]

	OR	95% CI	P-value
Clinical depression	4.03	3.87–4.20	<.001
Comorbidity[a]	1.18	1.16–1.19	<.001
Aspirin	1.15	1.09–1.19	<.001
HF severity[c]	1.10	1.09–1.12	<.001
Spironolactone	1.07	1.03–1.11	<.001
Statins	1.05	1.00–1.09	.028
Socio-economic status	1.03	1.01–1.04	<.001
Age	1.01	1.00–1.02	<.001
Ischemic etiology	1.00	.97–1.04	.86
Hospitalization days	.99	.99–1.00	<.001
ACE-inhibitors	.87	.84–.90	<.001
Beta-blockers	.83	.80–.86	<.001
Sex (males)	.59	.57–.61	<.001

[a] The Charlson Comorbidity Index was entered as a nominal variable (see Table 1).
[b] n = 120,453 due to missing data on predictor variables.
[c] According to average daily dosage of loop diuretic (furosemide) in the first 90 days after discharge (group 1, 0–39 mg; group 2, 40–80 mg; group 3, 81–160 mg; group 4, >160 mg).

3.5. Antidepressant groups and all-cause and CV mortality

In order to examine whether groups of anti-depressants (i.e., TCA, SSRI, other (tetracyclic, NaSSA, SNRI) were associated with a differential risk for all-cause and CV mortality, a univariable Cox proportional regression hazard analysis was performed for patients using antidepressants, stratified by group of antidepressants, using no antidepressant use as the reference category. Use of SSRIs (HR: 1.53; 1.49–1.56, P < .001), TCAs (HR: 1.18; 1.12–1.24, P < .001), other antidepressants (HR: 1.50; 1.44–1.56, P < .001) and a combination of antidepressants (HR: 1.57; 1.49–1.67, P < .001) was associated with an increased all-cause mortality risk compared to no antidepressant use (Fig. 2). In adjusted analysis, there remained a significant increased all-cause mortality risk for all antidepressant groups (P < .001 for all) (Table 4). In relation to CV mortality the use of SSRIs (HR:0.89; 0.87–0.91, P < .001), TCAs (HR:0.90; 0.86–0.95, P < .001), other antidepressants (HR:0.78; 0.75–0.81, P < .001) and

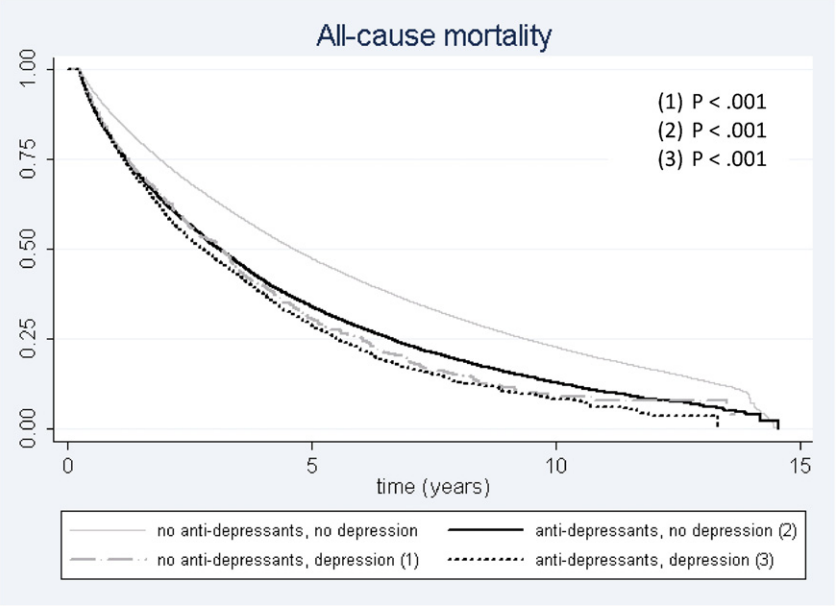

Fig. 1. Association between clinical depression and antidepressant use (at 90 days) and all-cause mortality (Kaplan Meier survival curve)*. *Reference group is no anti-depressant, no depression.

a combination of antidepressants (HR:0.79; 0.76–0.81, P < .001) was associated with a decreased risk, which remained similar after correction for socio-demographic, socio-economic and clinical covariates (Table 4).

A similar analysis was performed within the group of antidepressant users only (n = 19,348), with SSRI used as reference category. In univariable analysis, use of TCA (HR: 0.78; 0.74–0.82, P < .001) but not the use of other antidepressants (HR: 0.98; 0.94–1.02, P = .32) and a combination of antidepressants (HR: 1.03; 0.97–1.09, P = .39) was associated with a lower all-cause mortality risk compared to SSRI use (Fig. 3). In adjusted analysis, the use of TCAs remained associated with a lower all-cause mortality risk compared to SSRI use (P < .001), while neither the use of other antidepressants (P = .18) nor a combination of antidepressants (P = .45) was associated with all-cause mortality. There was no significant difference in the risk for CV mortality between the use of SSRIs and TCAs (HR: 1.02; 0.97–1.07, P = .46). However, other antidepressants (HR:0.88; 0.84–0.91, P < .001) and a combination of antidepressants (HR:0.86; 0.86–0.92, P < .001) showed a significantly decreased risk for CV mortality compared to the use of SSRIs.

Table 3
Association between clinical depression, antidepressant use (at 90 days) and all-cause and CV mortality (multivariable Cox proportional hazard analysis)[a,b].

Variables	All-cause mortality			CV mortality		
	HR	95% CI	P value	HR	95% CI	P value
Group						
No antidepressants, depression	1.25	1.15–1.36	<.001	1.17	1.14–1.20	<.001
Antidepressants, no depression	1.24	1.22–1.27	<.001	1.20	1.08–1.34	<.001
Antidepressants, depression	1.21	1.16–1.27	<.001	1.21	1.12–1.29	<.001
Sex (males)	1.27	1.25–1.29	<.001	1.17	1.15–1.20	<.001
Age	1.05	1.04–1.05	<.001	1.02	1.02–1.03	<.001
Socio-economic status[a]						
1	1.02	.99–1.04	.116	1.05	1.02– 1.07	<.001
2	1.03	1.01– 1.06	.002	1.10	1.07–1.13	<.001
3	.99	.97–1.01	.238	1.06	1.03–1.09	<.001
4	.86	.84–.88	<.001	1.05	1.02–1.08	<.001
Etiology	1.01	.99–1.02	.456	0.98	.96–1.00	0.07
HF severity[a]						
II	1.12	1.09–1.14	<.001	1.05	1.03– 1.08	<.001
III	1.33	1.30–1.36	<.001	1.20	1.17–1.23	<.001
IV	1.66	1.63–1.70	<.001	1.51	1.47–1.55	<.001
Beta-blockers	.82	.81–.84	<.001	1.09	1.07–1.11	<.001
ACE-inhibitors	.90	.80–.91	<.001	1.06	1.04–1.08	<.001
Spironolactone	1.12	1.10–1.14	<.001	1.17	1.14–1.20	<.001
Statins	.78	.76–.79	<.001	1.22	1.19–1.26	<.001
Aspirin	1.00	.99–1.02	.447	1.05	1.03–1.07	<.001
Hospitalization days	1.00	.99–1.00	<.001	0.99	.99–1.00	<.001
Comorbidity[a]						
1	1.36	1.34–1.38	<.001	1.18	1.15–1.20	<.001
2	1.58	1.54–1.61	<.001	1.34	1.30–1.38	<.001
3	1.68	1.64–1.73	<.001	1.41	1.36–1.46	<.001
4	1.99	1.92–2.03	<.001	1.63	1.56–1.70	<.001
≥5	2.20	2.12–2.27	<.001	1.76	1.68–1.83	<.001

[a] Reference group is lowest group (socio-economic status = 0, HF severity = 1 and comorbidity = 0).
[b] n = 120,453 due to missing data on predictor variables.

3.6. Antidepressant type and all-cause and CV mortality

Analyses of individual antidepressants showed that prescriptions of citalopram (HR: 1.20; 1.17–1.23, P < .001, HR:1.14; 1.11–1.18, P < .001), escitalopram (HR: 1.28; 1.19–1.37, P < .001, HR:1.58; 1.45–1.73, P < .001), venlafaxine (HR: 1.16; 1.07–1.25, P < .001, HR:1.12; 1.01–1.24, P < .001), and mirtazapine (HR: 1.21; 1.16–1.27, P < .001, HR:1.19; 1.12–1.26, P < .001) at baseline were associated with an increased all-cause and CV mortality risk, respectively. (Table 5).

Fluoxetine (HR: 1.13; 1.03–1.24, P = .01), sertraline (HR: 1.17; 1.11–1.24, P < .001), nortriptyline (HR: 1.16; 1.04–1.28, P = .005), amitriptyline (HR: 1.14; 1.06–1.21, P < .001), and duloxetine (HR: 1.39; 1.05–1.85, P = .02) were only significantly associated with increased all-cause mortality.

4. Discussion

To our knowledge, this is the first large-scale study using national registry data to examine the prevalence of antidepressant use during 5 years of follow-up, and the relationship between antidepressant use and all-cause and CV mortality in patients with HF, taking into account a clinical diagnosis of depression and stratifying analyses by antidepressant group and type. We found a relatively high prevalence of antidepressant use at baseline, which increased during the 5 years of follow-up, as was also found in a previous study [5]. In multivariable regression analyses, the prescription of antidepressants was not only

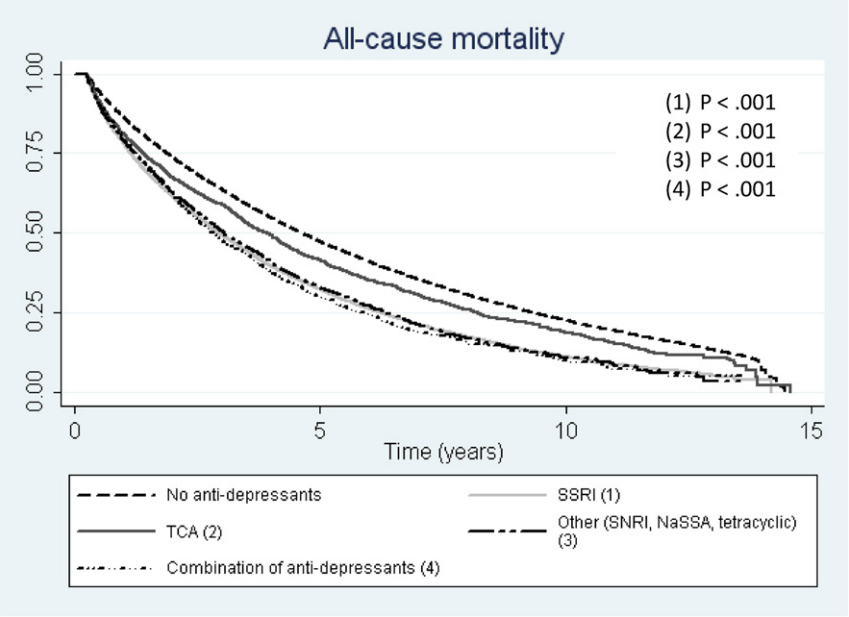

Fig. 2. Association between antidepressant groups (at 90 days) and all-cause mortality (Kaplan Meier survival curve)*. *Reference group is no antidepressants.

associated with a diagnosis of clinical depression, but also with older age, female sex, a higher severity of HF, higher comorbidity burden and less use of cardiac medications. There were no significant differences between patients with no antidepressant use and clinical depression versus patients using antidepressants without clinical depression in adjusted analyses. This suggests that antidepressant use might be a proxy for unregistered (sub)clinical depression *or* that antidepressant use per se could be responsible for the increase in all-cause and CV mortality risk. Given that 86.7% of the patients who were prescribed antidepressants at baseline had no diagnosis of clinical depression and antidepressant use was associated with increased mortality risk in this study, it seems timely to reconsider the administration of antidepressants in patients with HF, as the magnitude of this mismatch is not only surprising but also worrisome. Although antidepressants are prescribed for other disorders than depression, such as anxiety, fibromyalgia, chronic pain, and sleep disorders, our results suggest that their use might come at a considerable cost to patients.

No previous studies have examined the combined effect of clinical depression and antidepressant use, and studies which have investigated the separate risk of antidepressant use *or* depression found great variability in associated risk [5,6,9,10,16,17]. Despite these differences, the majority of studies found a significant increased mortality risk for both antidepressant use [6,7,9,10,16,17] and clinical depression, separately [5,6,17]. Some studies were not able to distinguish between the specific effect of the antidepressants on mortality in comparison to the effect of the disorder itself (i.e., depression), as they did not correct for depression [1,9,10]. Other studies examined the prevalence of depression by means of self-reported questionnaires, such as the Beck Depression Inventory (BDI) and the Geriatric Depression Scale [4,5,17]. The prevalence rates of depression in these studies were much higher as compared to the prevalence of clinical depression that we found in the current study (20–30% versus 3%, respectively). However, it is generally known that using self-report measures will lead to a higher prevalence as compared to a clinical diagnostic interview. Freedland et al. found that, despite the strong association between the BDI and the classifications of the Diagnostic and Statistical Manual of Mental Disorders, only 55% of patients scoring in the depressed range on the BDI had clinically significant depression according to the Diagnostic Interview Schedule, and 16% of patients classified as non-depressed on the BDI were depressed according to the Diagnostic Interview Schedule [18]. Besides the differences in the assessment of depression, there were also differences in the time of assessment, as they asked patients to complete depression measures during hospitalization. Furthermore, it could be that depression diagnosed in primary care is not always registered as clinical depression in the patient registry. Overall, this makes it difficult to directly compare the findings.

Subgroup analyses of antidepressants showed that the use of SSRIs, TCAs, SNRIs, other antidepressants or a combination of antidepressants at baseline significantly increased the risk for all-cause mortality but decreased the risk for CV mortality in this cohort of HF patients, also after correction for clinical depression.

This difference in mortality risk is interesting considering the fact that previous studies have found that TCAs, SSRIs, SNRIs and other antidepressants may have some pharmacological characteristics which could potentially increase CV mortality risk rather than decrease this risk. Antidepressants have been found to precipitate life-threatening arrhythmias, prolong the QT-interval, cause toxicity by drug-drug interactions, and show adverse physiological effects on heart rate variability, sympathetic control, hypertension and inflammation [3,13,19–22].

Alternatively, the elevated overall mortality risk could be explained by residual confounding due to unmeasured or unknown factors, such as poor self-care. Equally, it is plausible that a subset of patients suffers from treatment-resistant depression, in which the antidepressant is not capable of reducing the depressive symptoms sufficiently to decrease the mortality risk [23].

Table 4
Association between type of antidepressant (at 90 days) and all-cause and CV mortality (multivariable Cox proportional regression hazard analysis)[a,b,c].

Variables	All-cause mortality			CV mortality		
	HR	95% CI	P value	HR	95% CI	P value
Any SSRI	1.30	1.27–1.33	<.001	.88	.86–.90	<.001
Any TCA	1.23	1.07–1.19	<.001	.92	.88–.96	<.001
Any other antidepressant (SNRI, NaSSA, tetracylic)	1.41	1.36–1.47	<.001	.80	.77–.83	<.001
Combination of antidepressants	1.34	1.26–1.42	<.001	.79	.77–.82	<.001

[a] Reference group is no antidepressant use.
[b] n = 120,453 due to missing data for predictor variables.
[c] Analysis controlled for other variables: age, sex, socio-economic status, etiology, HF severity, comorbidity, statin, beta blocker, ACE inhibitor, spironolactone, aspirin, hospitalization (days), diagnosis of clinical depression.

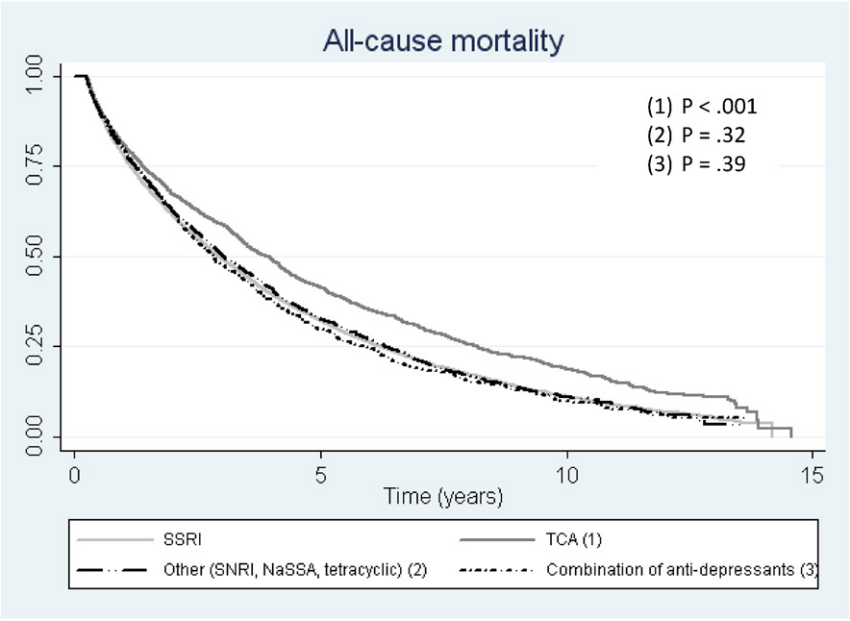

Fig. 3. Association between antidepressant groups (at 90 days) and all-cause mortality (Kaplan Meier survival curve)*. *Reference group is SSRI.

When we evaluated the mortality risk using SSRI use as reference category, the use of TCAs was associated with a 10% reduction in overall mortality risk in HF patients compared to the use of SSRIs, but showed no significant difference in relation to CV mortality. The results we found for overall mortality might be explained by a selection bias or unmeasured risk characteristics which may add to the differences between TCA and SSRI users.

Previous findings on the effect of individual antidepressants on the risk of mortality in HF patients were based on the use of antidepressants at any time during follow-up, and could therefore create discrepancies in relation to the outcomes of our study. We found that citalopram, escitalopram, venlafaxine, and mirtazapine at baseline were associated with an increased all-cause and CV mortality risk, respectively. Fluoxetine, sertraline, nortriptyline, amitriptyline, and duloxetine were only significantly associated with increased all-cause mortality. Overall, the finding that four of the SSRIs in our study were found to significantly increase the risk for mortality are surprising, since the use of SSRIs is considered relatively safe in comparison to the use of TCAs, especially for patients with HF [24]. Most other studies found no significant effect of SSRI use in adjusted analyses on mortality [5,6,8–12], or even a significant decrease in the risk of mortality [14,15]. Furthermore, two large randomized clinical trials that enrolled patients with coronary artery disease (i.e., Sertraline Against Depression and Heart Disease in Chronic Heart Failure SADHART and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial) found no safety issues with SSRI use [6] Diez-Quevedo et al. did found similar results for fluoxetine, but found no significant difference in the risk for sertraline and escitalopram and even a tendency towards a lower mortality risk for citalopram [5]. In relation to the TCAs, we found mixed findings in relation to mortality risk. This is similar to other findings with one study on post myocardial infarction (MI) patients finding a lower but non-significant risk for mortality [15] while other studies found no significant increase in the risk for mortality after a first-time MI or ischemic heart disease [5,8,10,11]. For the group of other antidepressants, only the

Table 5
Anti-depressant use (at 90 days) stratified by type in relation to all-cause and CV mortality (n = 120,453)[a,b].

Variables	Number of patients (%)	All-cause mortality			CV mortality		
Antidepressant use at 90 days		HR	95% CI	P value	HR	95% CI	P value
SSRIs							
Fluoxetine	622 (0.5%)	1.13	1.03–1.24	.01	.96	.86–1.09	.55
Paroxetine	570 (0.5%)	1.08	.98–1.20	.12	.95	.84–1.08	.44
Sertraline	1633 (1.4%)	1.17	1.11–1.24	<.001	1.07	1.00–1.15	.05
Citalopram	9372 (7.7%)	1.20	1.17–1.23	<.001	1.14	1.11–1.18	<.001
Escitalopram	1551 (1.3%)	1.28	1.19–1.37	<.001	1.58	1.45–1.73	<.001
TCAs							
Nortriptyline	556 (0.5%)	1.16	1.04–1.28	.005	1.11	.97–1.26	.12
Amitriptyline	1366 (1.1%)	1.14	1.06–1.21	<.001	1.08	.99–1.17	.09
Imipramine	289 (0.3%)	1.04	.90–1.21	.06	.97	.81–1.16	.72
Dosulepine	53 (0.05%)	.95	.68–1.32	.74	.60	.38–.93	.02
Tetracyclics							
Mianserine	26 (0.02%)	.98	.63–1.54	.93	1.05	.59–1.84	.87
SNRIs							
Venlafaxine	1034 (0.9%)	1.16	1.07–1.25	<.001	1.12	1.01–1.24	.03
Duloxetine	155 (0.1%)	1.39	1.05–1.85	.02	1.55	.95–2.53	.08
NaSSAs							
Mirtazapine	2789 (2.3%)	1.21	1.16–.1.27	<.001	1.19	1.23–1.26	<.001

[a] Reference group is no antidepressant use.
[b] Multivariable Cox proportional regression analysis adjusting for age, sex, socio-economic status, etiology, HF severity, comorbidity, statins, beta blockers, ACE-inhibitors, spironolactone, aspirin, hospitalization (days), and a diagnosis of clinical depression.

study by Monster et al. found a protective effect in relation to the risk of MI [12], with most other studies finding no significant difference in risk of use of other antidepressants in relation to MI [11,15], ischemic heart disease [10] or mortality [8].

In relation to the SNRIs and NaSSAs, venlafaxine, duloxetine and mirtazapine were also examined in previous studies in which no significant difference in risk on mortality was found [5,10].

4.1. Limitations

The results of the current study should be interpreted with the following limitations in mind. The main limitation is inherent in the observational nature of the study, with lack of information on certain clinical variables (e.g. left ventricular ejection fraction, New York Heart Association (NYHA) functional classification, smoking, alcohol consumption, and body mass index). Furthermore, there was a large discrepancy between the number of patients receiving antidepressants in comparison to the number of patients having a clinical depression. It could be that depression was diagnosed in primary care and therefore not registered in the national patient registry. Therefore, prescription of antidepressants could be a proxy for (sub)clinical depression. Although this study showed a substantially higher prevalence of clinical depression and use of antidepressants among women than among men, this study did not take into account the gender differential in this cohort of HF patients. Future studies are warranted to examine this gender differential in more detail, especially since some studies have raised the possibility that antidepressants may work somewhat differently in men and women. Exposure to antidepressants was measured only once (i.e., at 90 days post HF diagnosis), with the risk that study results could have been biased towards the null because a patient's exposure to medication may change over time. This approach was chosen, as we did not have information on the duration of antidepressant treatment use nor on the dosage. Furthermore, recorded prescriptions of antidepressants are not necessarily equivalent to adherence with treatment with consequences to prognosis, as shown in our study. Others have shown that non-adherent and poor adherent patients have no protective effects of antidepressant use and are more likely to die prematurely, as compared to patients who have moderate and high adherence levels.

5. Conclusion

In the current study, we found a high prevalence of antidepressant use in HF patients, with and without a diagnosis of clinical depression, subsequent to hospital discharge. Use of antidepressants increased over time after diagnosis with HF, and use of antidepressants after hospital discharge was significantly associated with a higher all-cause mortality risk, even when adjusting for socio-demographic and clinical variables and diagnosis of depression. These results highlight the importance of further examining the antidepressant prescription pattern in patients with HF patients, especially in those without a clinical depression. Future research should also seek to identify the unique pharmacological properties of individual antidepressants, as this may be crucial for understanding the antidepressant effects on cardiac function and mortality.

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Disclosures

All authors have no disclosures or conflict of interest.

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