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The Relationship Between Valproate and Lamotrigine/Levetiracetam Use and Prognosis in Patients With Epilepsy and Heart Failure: A Danish Register-Based Study

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ABSTRACT

Objective: To compare the hazard for all-cause mortality and mortality due to heart failure (HF) between valproate (VPA) and levetiracetam (LEV)/lamotrigine (LTG) users in patients aged ≥ 65 with comorbidities of epilepsy and HF.

Methods: This was a cohort study using Danish registers during the period from January 1996 to July 2018. The study population included new users of LTG, LEV or VPA. A Cox regression model was used to compute crude and adjusted hazard ratios for the outcome, using an intention-to-treat approach. Average treatment effects (eg, 1-year absolute risks), risk differences and the ratio of risks were computed using the G-formula based on a Cox regression model for the outcomes at the end of the follow-up period.

Results: We included 1345 subjects in the study population. VPA users (n = 696), when compared to LTG/LEV users (n = 649), had an increased hazard of mortality due to HF (hazard ratio [HR] 2.39; 95% CI 1.02−5.60) and to all-cause mortality (HR 1.37; 95% CI 1.01−1.85) in both crude and adjusted analyses. The 1-year absolute risks for all-cause mortality were 29% (95% CI 25%−33%) and 22% (95% CI 18%−26%) for VPA and LTG/LEV users. For mortality due to HF, 1-year absolute risks were 5% (95% CI 3%−7%) and 2% (95% CI 1%−4%) for VPA and LTG/LEV users. The average risk ratio, with LTG/LEV as the reference group, was 1.31 (95% CI 1.02−1.71) for all-cause mortality and 2.35 (95% CI 1.11−5.76) for HF mortality.

Conclusion: In older people with HF and epilepsy, treatment with VPA was associated with a higher risk of all-cause and HF mortality compared to treatment with LTG and LEV. (*J Cardiac Fail 2021;00:1−9*)

Key Words: Epilepsy, antiseizure medications, heart failure, older patients, prognosis.

Lay Summary

Cardiovascular diseases cause almost 50% of new-onset epilepsies in older individuals. The coexistence of these diseases represents a complex clinical scenario because medications used to treat seizures have negative effects on the heart. Lamotrigine, levetiracetam and valproate may represent the treatment individuals may receive after being diagnosed with epilepsy. In this study, we found that valproate use was associated with higher rates of mortality due to all causes and to heart failure when compared with the other 2 medications during the first year of treatment. These results may help clinicians to prioritize which drugs should be used when the final goal is improving the odds of survival.

Almost 50% of the causes of new-onset epilepsy in individuals aged 65 or older are caused by cardiovascular diseases and, more specifically, by stroke.[1] Cardiovascular risk factors leading to stroke are commonly associated also with the occurrence of heart failure (HF). Therefore, epilepsy and HF can commonly co-occur in this age group.[2] The coexistence of these diseases represents a complex clinical scenario because antiseizure medications have established cardiac effects,[3] which include proischemic effects and changes in atrial-ventricular conduction due to disorders of electrolytes (eg, sodium) and modulation of ion channels in the membranes and, more specifically, the sodium channels that modify the gating function.[3] These effects on the heart may lead to alteration of cardiac rhythm, blood pressure and, in the most extreme cases, HF.[3]

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Among antiseizure medications recommended in older patients with epilepsy, lamotrigine (LTG) is the drug of choice according to the clinical guidelines.[4,5] Levetiracetam (LEV) is another recommended drug both in the clinical guidelines as well as by experts[1,6] because of its efficacy and limited drug-drug interactions. Valproate (VPA) is an older common therapeutic option for epilepsy in older patients because of its broad spectrum of mechanisms of action and its rapid titration.[5] Personalized treatment choices are often made in the pharmacological treatment of seizures, and medications are chosen on a case-by-case evaluation based on the individual risk for adverse drug reactions and drug-drug/drug-disease interactions.[4,7,8] Contraindications may be a key element in guiding the choice of antiseizure medications for older patients. VPA is contraindicated in individuals with medical histories of disorders of the urea cycle, individuals with extensive pancreatic or hepatic dysfunction, cases of porphyria, and in those who have had coexposure to carbapenems or mefloquine. LEV is contraindicated in individuals with pancytopenia or suicidal ideation, whereas LTG is contraindicated in individuals with medical histories of Stevens-Johnson syndrome or drug reactions involving eosinophilia or systemic symptoms.[8,9]

LTG, LEV and VPA have different pharmacodynamics profiles. LTG has high selectivity for sodium channels and voltage-activated calcium-gated channels, and it can stabilize neuronal membranes in the presynaptic neuron which, in turn, determine reduced glutamate release.[10] LEV exerts its antiseizure effects through the inhibition of N-type Ca2 + currents and reduced mobilization and release of Ca2+ from intraneuronal stores. Additionally, LEV modulates the exocytosis of several neurotransmitters, including GABA (γ aminobutyric acid), through the synaptic vesicle protein 2A, a protein that mediates the fusion of vesicles containing neurotransmitters to the neuron plasmatic membrane during exocytosis.[11] VPA's antiseizure mechanisms of action involve modulation of GABA levels and blocking of voltage-gated ion channels in the central nervous system along with the inhibition of histone deacetylase.[12]

Because of their different pharmacodynamic properties, which involve the modulation of ion channels, LTG, LEV and VPA have differing profiles of cardiovascular safety; LEV is the drug with the fewest recognized cardiac effects.[3] In particular, LEV use has been previously associated with the rare occurrence of QT prolongation.[13−15] LTG is known to modulate cardiac conduction, whereas VPA might cause cardiac failure, which may be of high clinical relevance in individuals with concurrent HF.[3] Considering their not-negligible cardiovascular effects, it is crucial to understand whether the choice of antiseizure medication in patients with epilepsy and concurrent HF may influence their overall prognosis.[16,17] Therefore, to overcome these gaps in knowledge, this study aimed to compare the hazards of all-cause and HF mortality between VPA and LEV/LTG users in patients with epilepsy and concurrent HF.

Methods

Study Design and Setting

The study is a registry-based cohort study using Danish administrative registers from January 1996 through July 2018.

Data Source

All residents in Denmark receive a civil registration number, which is a unique identifier that can be used to retrieve information on an individual level from the Danish administrative registers. In this study, we used the Danish Family Income Register[18] to retrieve information about patients' incomes, the Danish National Patient Registries[19] to collect information about hospital/ambulatory diagnoses and the Danish Prescription Registries[20,21] to identify prescription redeemed from public pharmacies. Additionally, we used the Danish Cause of Death Register[22] to assess the dates and causes of death, the Danish Civil Registration System[23] to retrieve information about birth date and sex, and the Danish Education Register[24] to identify the highest achieved education levels of patients.

Study Population

The study population was composed of all the Danish citizens aged 65 or older with HF and epilepsy who, during the study period, redeemed their first prescriptions for LTG, LEV or VPA (ie, new users). Patients were considered to have HF if they were admitted to the hospital or were ambulatory and had the International Classification of Diseases, 10th Revision (ICD10), code I50 and all subcategories of I50. Analogously, patients were classified as having epilepsy if they were admitted to the hospital or were ambulatory and had the ICD10 code G40. The positive predictive value of both diagnoses in Danish registers is high. The positive predictive value of diagnoses of HF is 83.6% (95% CI: 80.1%–86.7%), whereas of epilepsy, it is 81% (95%CI: 75%−87%) in hospitalized patients.[25,26] Consequently, the risk of misclassification of HF and epilepsy diagnoses for these patients is low. We included only patients who had redeemed their first antiseizure medications following their first epilepsy diagnosis so as to mitigate the possibility of misclassification of exposure, considering that antiseizure medications have approved indications for use in issues other than epilepsy. For each patient included in the study population, the date of the first redemption of the prescription for antiseizure medication (ie, LEV, LTG or VPA) was used as the index date or, rather, the time at which we started following-up patients in the Danish registers. A 1-year washout period before the index date was used to define new users of LTG, LEV or VPA. The study population was divided into 2 cohorts: LTG/LEV users and VPA users.

Follow-up period

Patients were followed for 365 days from the index date until they were censored at the occurrence of the study

outcomes, the end of the follow-up period, death, or permanent emigration. The study outcomes were all-cause mortality and HF mortality within 365 days from the index date. The follow-up period was set to 1 year, considering that the antiseizure medications under investigation have cardiovascular effects that can occur during the first year of treatment.[3]

Variables

The operative definitions of the variables codifying exposure, outcome and potential confounders were selected based on clinical experts' suggestions and by systematically screening the scientific literature; they are provided in Supplementary Table 1. (Methodological details are provided in Supplementary Table 2.) Other potential confounders in this study were selected on the basis of a data-driven approach. In particular, for the covariates identified using a data-driven approach, we followed the approach described by Schneeweiss et al.[27] for constructing the high-dimensional propensity score (hdPS), limiting our data sources to prescriptions redeemed in public pharmacies[20,21] and hospital admissions/hospitalizations,[19] according to Hallas and Pottegård.[28] The hdPS include all causes of hospital admission/hospitalization or current pharmacological treatments and their frequencies, with the highest impact for confounding adjustment. Consequently, the hdPS accounts also for polytherapy with antiseizure medications and other treatments for HF. Supplementary Fig. 2 shows 150 variables that can impact and confound adjustment.

Statistical Analysis

The baseline clinical and demographic characteristics suggested as potential confounders by clinical experts were compared between cohorts. Differences in continuous variables were reported as mean, standard error or median and interquartile (IQR) ranges (in case of nonparametric distributions of continuous variables). For each outcome, we presented the total number of events, the person-years of follow-up, the incidence rates, and the hazard ratios among those exposed to VPA or LTG/LEV. We identified 718 potential confounders by using the 3 approaches mentioned above under Variables to compute the hdPS for the exposure. A Cox regression model was used to compute adjusted hazard ratios for the study outcomes between the cohorts using the group treated with LTG/LEV as the reference group and adjusting for deciles of hdPS. Proportional hazards tests and diagnostics based on weighted residuals were used to evaluate whether the assumption of proportionality of hazard was held as described by Therneau et al.[29] Smoothed cumulative hazard plots for the study outcomes were drawn for the 2 treatment groups to compare the cumulative hazard. The Gray test was used as a statistical test to evaluate the divergences of the cumulative hazard functions.[30] Conditional inference, which is a machine learning approach to partition recursively the predictors most closely associated with the outcomes, was used to investigate nonlinear interactions among covariates, with the final goal of identifying subgroups of interest, as described elsewhere.[31−34] All analyses were conducted using an intention-to-treat approach.[35] Adherence to treatment with antiseizure medications was evaluated using the continuous multiple interval measures of medication availability/gaps (CMA5) from AdhereR. Treatment persistence was assessed as a continuous treatment episode with a maximum permissible gap of 90 days among consequently redeemed prescriptions.[36] SAS statistical software (version 9.4, SAS Institute, Cary, NC) and R (version 3.6.1, R Development Core Team) were used for the data management and analysis, respectively.

Sensitivity Analyses. In the first sensitivity analysis, to guarantee exchangeability between VPA and LTG/LEV users, hdPS was used to match, 1:1, patients who were exposed to LTG/LEV with those who were exposed to VPA by using the nearest neighbor algorithm (caliper: 0.05). To evaluate exchangeability, the density function of the propensity score for both VPA and LTG/LEV users was plotted, and we checked to see whether the overall overlapping was greater than 80%. A Cox regression model was used to compute the hazard ratio for the study outcomes between the cohorts, using the group treated with LTG/LEV as the reference group. In the second sensitivity analysis, average treatment effects (1-year absolute risk), risk difference and the ratio of risks were computed using the G-formula based on a Cox regression model for all-cause or HF mortality at the end of the follow-up period (eg, 365 days from the index date), as described by Gerds and colleagues.[37] We used 1000 bootstrap replications to compute the confidence intervals.

Ethics

The study did not need ethical approval or patient consent because Danish register-based cohort studies are exempted. Patient records and information before the analysis were pseudonymized. The University of Copenhagen and Statistics Denmark (project #707278) have appropriate data approval from the Regional Capital Area Data Protection Agency to facilitate the conduct of the present study.

Results

Baseline Characteristics of the Study Population

In total, 1345 patients were included in the study population, of whom 973 (72.3%) had medical histories of cerebrovascular accidents (strokes or transient ischemic attacks) or related cardiovascular risk factors: hypertension, 56.1%; coronary heart disease, 42.9%; myocardial infarction, 23.1%; dyslipidemia, 29.4%; atrial fibrillation, 48.4%. Among other pathologies associated with epilepsy, 11.9% of patients had dementia. In the study population, less than 5% of patients had hepatic disorders, whereas 12.6% had chronic kidney diseases. Patients exposed to VPA or LTG/LEV had, in the median, their first diagnosis of HF 3.53 (IQR 1.13−7.73 years) and 4.06 years (IQR 1.23−8.36

years) before the index date, respectively. In both cohorts, patients received antiseizure medications following the diagnosis of epilepsy (0.03 years, IQR 0.01−0.15 years, for LTG/LEV users, and 0.04 years, IQR 0.01−0.27 years, for VPA users). These results justify the 1-year wash-out period for defining new users of antiseizure medications and reduce the risk of misclassification of exposure due to usage of antiseizure medications for other indications.

The patients exposed to VPA had a mean age of 77.9 years and were statistically significantly older than LTG/LEV users (mean age 76.5 years). The 2 cohorts had a similar sex distribution; the proportions of men among VPA and LTG/LEV users were 54.0% and 57.5%, respectively. Patients exposed to LTG/LEV, when compared to VPA users, had a higher proportion of medical histories of myocardial infarction (26.3% and 20.1%), lipid disorders (36.4% and 23.0%), thyroid disorders (8.0% and 6.6%), hepatic disorders (5.2% and 3.2%), chronic obstructive pulmonary disease (22.2% and 20.5%), and chronic kidney disease (13.6% and 11.8%). Additionally, they had a higher proportion of individuals with anemia (1.5% and 1.1%) who had undergone surgery for coronary artery bypass graft (11.1% and 5.9%), percutaneous coronary intervention (13.7% and 7.6%), or valve surgery (9.7% and 3.9%), or who were receiving angiotensin-converting enzyme inhibitors (40.7% and 31.9%), angiotensin II receptor blockers (14.5% and 10.6%), or HMG-CoA reductase inhibitors (51.3% and 35.6%) (Table 1).

In all, 548 patients were included in the matched study population, of whom 274 were exposed to VPA, and 274 were exposed to LTG/LEV. Exchangeability was reached, considering that 85% of the hdPS density functions overlapped between the cohorts (Fig. 1). The patients exposed to VPA had a mean age of 76.6 years; the LTG/LEV users had a mean age of 76.5 years. The 2 cohorts had similar proportions of men (59.1% and 58.4%, for VPA and LTG/LEV users, respectively).

We did not observe differential treatment discontinuation/switch patterns among individuals exposed to various antiseizure medications. In total, the study population had adherence of 100% (IQR 100%–100%) with no intercohort variation. In all, 17 of 1345 (1.26%) switched antiseizure medication in the observational window.

All-cause and HF mortality

The person-years of follow-up and the number of patients with the study outcomes are provided in Table 2. The top 7 causes of death were stroke (16%), HF (12%), pneumonia (9%), respiratory failure (8%), ischemic heart disease (5%), unspecified cardiac disorders (3%), and cardiac arrest (2 %).

During the first year of exposure to antiseizure medications, VPA users, when compared to LTG/LEV users, had a statistically significant higher cumulative hazard for HF and all-cause mortality (Fig. 2). Analogously, VPA use conferred increased hazards of HF mortality (crude: HR 3.04; 95% CI 1.45−6.49; adjusted: HR 2.39; 95% CI 1.02–5.60) and all-cause mortality (crude: HR 1.77; 95% CI 1.38–2.15; adjusted: HR 1.37; 95% CI 1.01–1.85). For all-cause mortality, the subgroup aged 75 years, exposed to VPA and redeeming large prescriptions of paracetamol, was identified to be the subgroup with the highest proportion of deaths (80 death/153 patients; 52%; *P*value 0.040). For HF mortality, no statistically significant interactions among study variables were identified.

In the first sensitivity analysis performed on the matched cohort, the results were consistent for all-cause mortality (HR 1.63; 95% CI 1.15–2.33). For HF mortality, we were not able to provide reliable results because the number of patients having the outcome among LTG/LEV users was lower than 5.

In the second sensitivity analysis, the 1-year absolute risk for all-cause mortality was 29% (95% CI 25%–33%) and 22% (95% CI 18%–26%) for VPA and LTG/LEV users, respectively. For HF mortality, the 1-year absolute risk was 5% (95% CI 3%–7%), and the risk was 2% (95% CI 1%–4%) for VPA and LTG/LEV users, respectively. The risk difference (VPA vs LTG/LEV) for all-causes and HF mortality were 7% (95% CI 1%–13%) and 3% (95% CI 1%–5%), respectively. The average risk ratio, with LTG/LEV as the reference group, was 1.31 (95% CI 1.02–1.71) for all-cause mortality and 2.35 (95% CI 1.11–5.76) for HF mortality.

Discussion

One of the fastest-growing age groups globally is patients aged 65 and older, which makes them very relevant and important to study from a public health perspective.[1] Epilepsy in older people with cardiovascular comorbidities, furthermore, is a common combination of diseases that is relatively under-researched.[1]

In this study, we investigated the commonly observed population of older patients with epilepsy and HF. The study population is closely representative of the general population of individuals having this combination of diseases; they have a prevalence of etiological factors and comorbidities that perfectly match those mentioned in the scientific literature. In particular, 72.3% of the patients had medical histories of cerebrovascular accidents (ie, strokes), which are the most well-known risk factors for the occurrence of epilepsy in older patients. Of note, this prevalence was higher (ie, 50%[1]) than those observed in the whole population of patients with epilepsy aged 65 or older. However, it is easy to believe that such a prevalence should be higher in patients having concurrent cardiovascular risk factors highly associated with stroke (ie, HF). In our study population, we observed that those patients taking VPA had an increased hazard of HF and all-cause mortality when compared to users of LTG or LEV. This was consistent in the sensitivity analysis, where we observed that VPA users had an increased all-cause mortality hazard ratio. This could not, however, be confirmed for HF mortality because the number of patients with the outcome was too low. We hypothesize that the cardiovascular effect of the antiseizure

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Level	LTG/LEV (n = 649)	VPA (n = 696)	*P* value
Age	Mean (SD)	76.5 (8.5)	77.9 (8.6)	0.002
Sex	Male	373 (57.5)	376 (54.0)	
	Female	276 (42.5)	320 (46.0)	0.223
Ulcer	Yes	58 (8.9)	88 (12.6)	0.036
Diabetes	Yes	165 (25.4)	170 (24.4)	0.719
Myocardial infarction	Yes	171 (26.3)	140 (20.1)	0.008
Thyroid disorders	Yes	52 (8.0)	46 (6.6)	0.377
Uricemia	Yes	37 (5.7)	38 (5.5)	0.941
Cancer	Yes	133 (20.5)	107 (15.4)	0.017
Cerebrovascular accidents	Yes	458 (70.6)	515 (74.0)	0.180
Arthritis	Yes	37 (5.7)	36 (5.2)	0.759
Dyslipidaemia	Yes	236 (36.4)	160 (23.0)	<0.001
Chronic obstructive pulmonary disorders	Yes	144 (22.2)	143 (20.5)	0.504
Asthma	Yes	43 (6.6)	43 (6.2)	0.823
Pulmonary heart disease	Yes	406 (62.6)	349 (50.1)	<0.001
Coronary heart disease	Yes	386 (59.5)	382 (54.9)	0.100
Atrial fibrillation	Yes	335 (51.6)	316 (45.4)	0.026
Depression	Yes	70 (10.8)	54 (7.8)	0.068
Dementia	Yes	73 (11.2)	160 (11.9)	0.532
Hepatic disorders	Yes	34 (5.2)	22 (3.2)	0.077
Anemia	Yes	10 (1.5)	8 (1.1)	0.699
Respiratory disease	Yes	393 (60.6)	349 (50.1)	<0.001
Chronic kidney disease	Yes	88 (13.6)	82 (11.8)	0.369
Ventricular arrhythmia	Yes	27 (4.2)	32 (4.6)	0.796
Coronary arteria bypass graft	Yes	72 (11.1)	41 (5.9)	<0.001
Percutaneous coronary intervention	Yes	89 (13.7)	53 (7.6)	<0.001
Valve surgery	Yes	63 (9.7)	27 (3.9)	<0.001
Pacemaker	Yes	216 (33.3)	272 (39.1)	0.031
Angiotensin converting enzyme inhibitor	Yes	264 (40.7)	222 (31.9)	<0.001
Angiotensin II receptor blocker	Yes	94 (14.5)	74 (10.6)	0.040
Angiotensin II receptor blocker + diuretic	Yes	26 (4.0)	22 (3.2)	0.492
High-ceiling diuretics	Yes	353 (54.4)	427 (61.4)	0.011
Potassium sparing agent	Yes	92 (14.2)	123 (17.7)	0.094
HMG-CoA reductase inhibitor	Yes	333 (51.3)	248 (35.6)	<0.001
Cardiac glycoside	Yes	148 (22.8)	213 (30.6)	0.002
Antiarrhythmics class 3	Yes	18 (2.8)	23 (3.3)	0.684
Organ nitrates	Yes	101 (15.6)	129 (18.5)	0.169
Insulin-fast acting	Yes	23 (3.5)	22 (3.2)	0.811
Insulin injection intermediate	Yes	16 (2.5)	37 (5.3)	0.011
Biguanide	Yes	63 (9.7)	45 (6.5)	0.037
Sulfonylurea	Yes	30 (4.6)	52 (7.5)	0.039
Anticoagulants	Yes	236 (36.4)	167 (24.0)	<0.001
Platelet aggregation inhibitors	Yes	405 (62.4)	447 (64.2)	0.525
Acetylsalicylic acid	Yes	319 (49.2)	367 (52.7)	0.209
Proton pump inhibitor	Yes	225 (34.7)	227 (32.6)	0.460
Antipsychotics	Yes	51 (7.9)	89 (12.8)	0.004
Atypical depression	Yes	58 (8.9)	65 (9.3)	0.872
Serotonin-norepinephrine reuptake inhibitor	Yes	24 (3.7)	11 (1.6)	0.023
Selective serotonin reuptake inhibitor	Yes	162 (25.0)	201 (28.9)	0.120
Antibiotics	Yes	290 (44.7)	287 (41.2)	0.222
Opioids	Yes	185 (28.5)	176 (25.3)	0.204
Nonsteroidal anti-inflammatory drugs	Yes	71 (10.9)	92 (13.2)	0.232

LEV, levetiracetam; LTG, lamotrigine; VPA, valproate.

medications may have contributed to the negative outcome of the patients. It has been proved that VPA use is associated with the upregulation of antidiuretic hormone release in the renin-angiotensin-aldosterone system.[38] With the increased amount of antidiuretic hormone, renin release is induced which, in turn, increases the production of angiotensin 2. This is known to cause a loop, increasing the upregulation of the production of angiotensin 2, which is a key pathophysiological biomarker of HF.[39,40] It has been proved that blocking the production of angiotensin 2 is associated with an increased survival time in patients with HF. Accordingly, the first-line drug for treating HF is angiotensin-converting-enzyme inhibitors,[41] which protect against mortality by blocking the anabolism of angiotensin 2[42] and increase the survival time by 50%, according to the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial.[43] In a recent meta-analysis that included 38 studies (47662 patients with HF) and investigated the role of angiotensin-converting-enzyme inhibitors in survival, the all-cause mortality rate was reduced by 11% in those treated with this drug class.[44] We speculate that VPA may have promoted an increase in mortality rates because of its unique ability (among antiseizure medications) to induce alteration of the cardiac conduction through

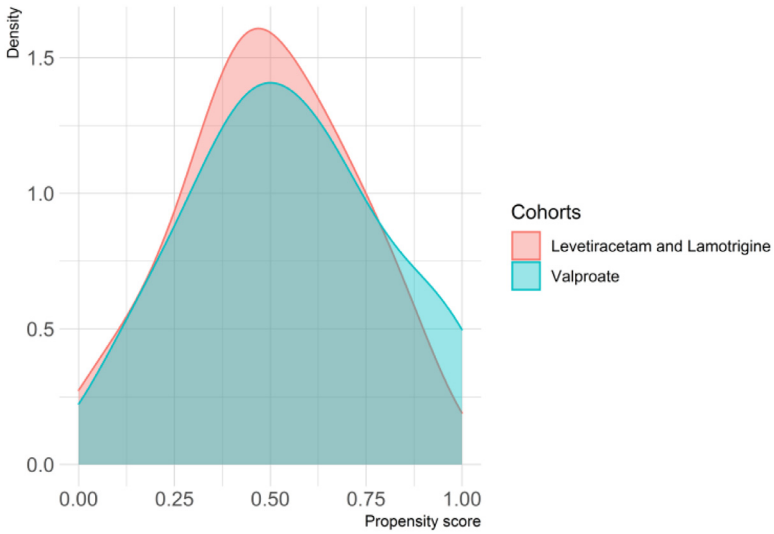

Fig. 1. Density function of the propensity score for the matched cohorts.

blockage of the voltage-gated sodium channels, to reduce blood pressure and proischemic effects (eg, angina or myocardial infarction), and to upregulate the anabolism of angiotensin 2, which are all known risk factors for poor prognosis in patients with HF.[3,41,45] The above-mentioned hypotheses are in line with the top-7 observed causes of death. Regarding the reduced risk of mortality due to HF observed among LEV/LTG users, we hypothesized that the reduced mortality due to HF with the use of these medications is attributable to their rare and minimal effects on the cardiovascular system.[3] In fact, LEV has a pronounced tropism for calcium channels in the central nervous system (ie, N-type).[13]

Strengths and Limitations

The study is of an observational nature and, therefore, we cannot exclude the possibility that observed associations may be biased due to unmeasured confounders, such as proxies of the severity of HF and left ventricular ejection fraction, stage of HF, natriuretic peptides, severity of the epilepsy, smoking, and body mass index.[46] However, there is no current evidence suggesting that VPA users should include a greater proportion of patients with higher severity of HF, smokers and/or obese patients. Another limitation of this study is that the characteristics of seizures were unknown. It is expected that prescribers may be more likely to prescribe VPA for generalized as opposed to partial seizures. Additionally, it is unlikely that we were able to capture clinical nuances in choosing VPA over LTG/LEV in our data sources and, as mentioned above, we cannot exclude residual confounding or unaccountable confounders. The strengths include hdPS, which has shown advantages in confounding adjustments when compared to predefined covariates suggested by clinical experts.[27,47] This has further been confirmed to work in a Danish setting.[28] In this regard, it should be mentioned that because we used all redeemed prescriptions and hospital admissions, including the intensity of their occurrence, for the construction of the hdPS, they might have served as proxies of disease severity for HF and epilepsy. Another strength is the inclusion of the entire Danish population aged 65 or older, which minimized the potential risk of selection bias. Additionally, another strength is the use of Danish registers,

Table 2. Crude and Adjusted Hazard Ratio for the Outcomes of the Cohorts

Cohorts	Number of patients	Number of events	Person-years of follow-up	Hazard ratio (95% confidence interval)	Outcome	Type
VPA	696	220	560	1.77 (1.38−2.15)	All-cause mortality	Crude
LTG/LEV	649	130	586	Reference group	-	-
VPA	696	220	560	1.37 (1.01–1.85)	All-cause mortality	Adjusted
LTG/LEV	649	130	586	Reference group	-	-
VPA	274	84	222	1.63 (1.15−2.33)	Matched all-cause mortality	Adjusted
LTG/LEV	274	55	237	Reference group	-	-
VPA	696	32	560	3.04 (1.45–6.49)	HF mortality	Crude
LTG/LEV	649	11	586	Reference group	-	-
VPA	696	32	560	2.39 (1.02–5.60)	HF mortality	Adjusted
LTG/LEV	649	11	586	Reference group	-	-

HF, heart failure; LEV, levetiracetam; LTG, lamotrigine; VPA, valproate.

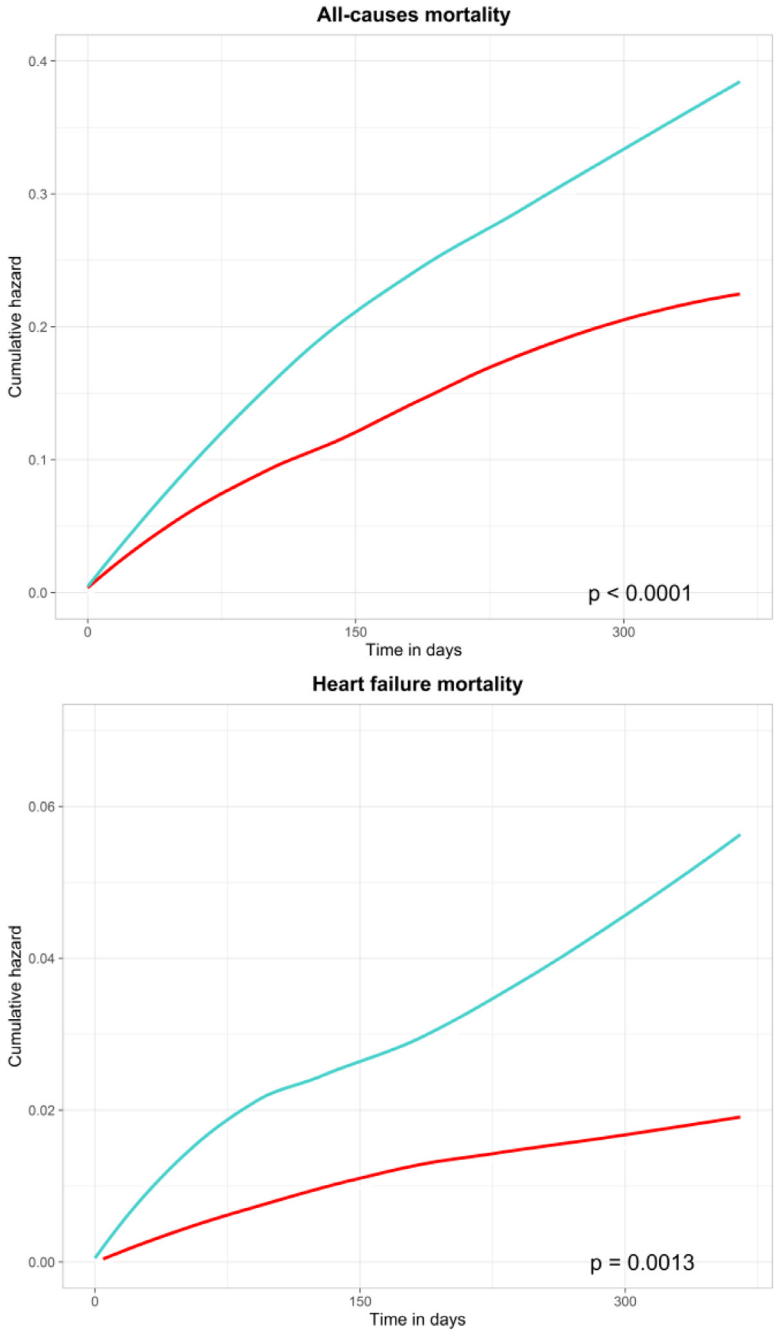

Fig. 2. Smoothed cumulative hazard plot for the study outcomes by cohorts. Red line, valproate users; blue line, lamotrigine/levetiracetam; *P* value was calculated using the Gray test.

which have a high internal and external validity for the investigated outcomes and exposures.

Conclusion

In conclusion, the choice of antiseizure medication may influence prognosis in patients with epilepsy 65 of age or older with HF as a comorbidity. In fact, this study suggests that treating epilepsy with VPA in patients with cardiovascular comorbidity is associated with a higher hazard of all-cause and HF mortality when compared to treatment with newer drugs, such as LTG and LEV. From a clinical perspective, these results are useful for deciding which antiseizure medication should be chosen for patients with epilepsy and concurrent HF. It is hoped that this study will spark new research to clarify these associations and to better characterize the cardiovascular risk associated with antiseizure medications in patients with epilepsy and concurrent cardiovascular diseases.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2021.07.020.

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