Epilepsy-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications in patients with Epilepsy

Tommaso Bucci, MD[a,b,†], Gashirai K. Mbizvo, MD, PhD[a,c,d,†], José Miguel Rivera-Caravaca, RN, PhD[a,e,f,†], Josephine Mayer, MBChB, MRes[a,c,d], Anthony G. Marson, MD[a,c,d], Azmil H. Abdul-Rahim, MD, PhD[a,g,h,+], and Gregory Y.H. Lip, MD[a,i,+,*]

From the [a] Liverpool Centre of Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK, [b] Department of General Surgery and Surgical Specialties "Paride Stefanini," Sapienza University of Rome, Rome, Italy, [c] Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK, [d] The Walton Centre NHS Foundation Trust, Liverpool, UK, [e] Department of Cardiology, Hospital Clínico Universitario Virgen de La Arrixaca, University of Murcia, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBERCV, Murcia, Spain, [f] Faculty of Nursing, University of Murcia, Murcia, Spain, [g] Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK, [h] Department of Medicine for Older People, Stroke Division, Whiston Hospital, St Helens and Knowsley Teaching Hospitals NHS Trust, Rainhill, UK and [i] Department of Clinical Medicine, Aalborg University, Aalborg Denmark.

Abstract: The risks of cardiovascular events (CVEs) in people with epilepsy (PWE) are not well understood. To establish the short- and long-term burden of CVEs in PWE. Electronic health records from a global federated health research network (TriNetX) were used to establish a cohort of PWE. Primary outcomes were: (1) the proportion of people experiencing a composite

† The authors contributed equally and considered as first authors.
+ joint senior authors.
*Corresponding authors: Gregory Y.H. Lip, Liverpool Centre for Cardiovascular Science, Institute of Life Course & Medical Sciences, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, UK. E-mail: gregory.lip@liverpool.ac.uk

Curr Probl Cardiol 2023;48:101868
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2023.101868

outcome of cardiac arrest, acute heart failure (HF), acute coronary syndrome (ACS), atrial fibrillation (AF), severe ventricular arrhythmia or all-cause death within 30 days of a seizure; and (2) the 5-year risk for a composite outcome of ischemic heart diseases, stroke, hospitalization, or all-cause death in the PWE experiencing early CVEs. Cox-regression analyses with propensity score matching was used to produce hazard ratios (HRs) and 95% confidence intervals (CI). In 271,172 PWE (mean age 50 ± 20 years; 52% females), the 30-day risk of CVEs following seizure was: 8.7% for the composite outcome, 0.9% for cardiac arrest, 0.8% for HF, 1.2% for ACS, 4.1% for AF, 0.7% for severe ventricular arrhythmias, and 1.6% for all-cause death. For the 15,120 PWE experiencing CVEs within 30 days of seizure, the 5-year adjusted risks for all composite outcomes measured were significantly increased (overall HR: 2.44, 95% CI 2.37-2.51), ischemic heart diseases HR 3.23 (95% CI 3.10-3.36), stroke HR 1.56 (95% CI 1.48-1.64), hospitalization HR 2.03 (95% CI 1.97-2.10), and all-cause death HR 2.75 (95% CI 2.61-2.89). The large proportions of PWE with active disease that experience CVEs and the poor long-term outcome associated suggest the existence of an "epilepsy-heart syndrome."—Epilepsy is associated with an increased risk of cardiovascular events.—This study clarifies the incidence and clinical outcomes associated with each cardiac complication in patients with epilepsy.—An integrated neurology and cardiovascular clinical service may be considered to counteract the risk of cardiovascular events in patients with epilepsy. (Curr Probl Cardiol 2023;48:101868.)

Key messages

- What's already known about this topic?
  Epilepsy is associated with an increased risk of cardiovascular events.
- What does this article add?
  This study clarifies the incidence and clinical outcomes associated with each cardiac complication in patients with epilepsy.
  An integrated neurology and cardiovascular clinical service may be considered to counteract the risk of cardiovascular events in patients with epilepsy.

Introduction

Epilepsy is associated with increased risk of cardiovascular events (CVEs) such as stroke, acute coronary syndrome (ACS) and sudden cardiac death.[1-5] The pathophysiological mechanisms underlying this are complex and multifaceted. People with epilepsy (PWE) may have reduced physical activity, less healthy diets, and increased stress, anxiety, and depression. These could impact on healthy lifestyle, facilitating the onset of arterial hypertension, obesity and diabetes mellitus.[6,7] Antiseizure medications can cause weight gain and elevated levels of cholesterol that may be responsible for an enhanced atherosclerotic burden.[8-10] Epilepsy may also manifest as a sign of vascular disease. In fact, almost 15% of the newly diagnosed epilepsy in adult patients are associated with previous stroke or can represent the first manifestation of a subclinical cerebrovascular atherosclerotic disease.[11,12]

A large network of cortical and subcortical brain regions (the central autonomic network [CAN]) controls cardiovascular functions via sympathetic and parasympathetic outflow. After an acute neurological injury, the damaged connections induce a local and systemic inflammatory response, potentially causing myocardial necrosis, microvascular dysfunction, coronary ischemia, heart failure (HF), arrhythmogenesis, or asystole.[13,14] Ictal asystole is strongly associated with right temporal lobe seizures, and may be a direct consequence of seizures stimulating the CAN or indirect effect of seizures (eg, catecholamine release) evoking the vasovagal reflex.[15,16] Ictal asystole is generally self-limiting owing to cerebral anoxia and ischemia caused by the asystole naturally terminating the seizure.[15,16] However, the postictal asystole associated with convulsive seizures carries a higher risk of fatality by interfering with postictal resumption of ventilation, perhaps leading to sudden unexpected death in epilepsy (SUDEP).[16] These and other mechanisms have led to a recently proposed concept of "the Epileptic Heart," with much of the focus centered on sudden cardiac death.[14]

Nevertheless, we still need to clarify the incidence and clinical outcomes of cardiac complications in PWE if we are to develop strategies to predict and prevent morbidity and mortality. We report a large population-based propensity-matched analysis of a global federated health network describing the proportion of PWE experiencing early CVE within 30 days after a seizure-related healthcare consultation, and the longer-term risks within 5 years of cardiac morbidity or death in these people.

Methods

Study Design

This was an observational study conducted within TriNetX, a global federated health research network with access to electronic medical records (EMRs) from academic and community hospitals covering approximately 80 million individuals, mainly located in the United States. Within this network, available data include demographics, diagnoses using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, and medications. More information can be found online (https://trinetx.com/company−overview/).

Cohort

The searches on the TriNetX online research platform were performed on December 28, 2022 for individuals aged ≥18 years with diagnosis of epilepsy with recurrent seizures (ICD-10 G40 code) reported at least 2 times, treated with antiseizure medications (Supplementary Table 1). At the time of the search, 63 participating health care organizations had data available for individuals who met the study inclusion criteria. The baseline index event was the date of the first G40-coded activity reported in the TriNetX platform. G40-coded activity was a seizure-related healthcare consultation. The comorbid diagnoses registered before the index event were the individual's baseline characteristics. The early (30-day) CVEs and the long-term (5-year) clinical outcomes were identified via ICD-10-CM codes as follows: I46 for cardiac arrest, I50.21, I50.31, I50.811, I50.33, I50.23, I50.43, I50.813 for acute HF, I20.0 and I21-I24 for ACS, I48 for AF, I47.2 for ventricular tachycardia and I49.0 for ventricular fibrillation or flutter (severe ventricular arrhythmia), and ischemic heart disease (I20-I25). Hospitalization and all-cause death were identified with specific variables coded by the TriNetX platform. All the ICD-10-CM codes used for the early CVEs and long-term clinical outcome diagnosis are reported in the Supplementary Table 2.

Outcomes and Statistical Analyses

Primary outcomes measured after the first seizure-related healthcare consultation (ie, a G40-coded event) amongst PWE were: (1) the proportion experiencing a composite outcome of cardiac arrest, HF, acute coronary syndrome (ACS), atrial fibrillation (AF), severe ventricular arrhythmia (ventricular tachycardia, fibrillation or flutter) or all-cause

death within 30 days; and (2) the 5-year risk for a composite outcome of ischemic heart diseases, stroke, hospitalization or all-cause death in the PWE experiencing CVEs within 30 days. The 5-year risk for the composite outcome was compared to a matched control group of PWE without experiencing CVEs within 30 days of the first seizure-related healthcare consultation.

Secondary outcomes included the 5-year risk of adverse outcomes associated with each type of CVE occurring within 30 days of the first seizure-related healthcare consultation. For this analysis we created 5 different subgroups of PWE based on the type of 30-day CVE. We then compared these subgroups with matched cohorts of the following: (1) PWE not experiencing the 30-day CVE outcome, and (2) patients without epilepsy with each type of CVE.

Baseline characteristics were compared using chi-squared tests for categorical variables and independent-sample t-tests for continuous variables. Standardized mean differences (Std diff.) were used to show the distribution of demographic and clinical data among the groups and calculated as the difference in the means or proportions of a particular variable divided by the pooled estimate of standardized differences for that variable. Propensity score matching (PSM) 1:1 was used to control the differences in the comparison cohorts. Cohort matching was performed for age at index event, sex, ethnicity, arterial hypertension, diabetes, chronic ischemic heart disease, chronic HF, cerebrovascular disease, cardiovascular procedures (including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures), and cardiovascular medications (β-blockers, antiarrhythmics, diuretics, lipid lowering drugs, antianginals, calcium channel blockers, and angiotensin-converting enzyme inhibitors). These variables were chosen because they may influence clinical outcomes. Any baseline characteristic with an Std diff.$<$0.100 was considered well matched. After PSM, Cox-regression proportional hazard models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the 5-year risk of primary and secondary outcomes. To investigate the primary outcome, PWE with CVEs within 30 days of the first seizure-related healthcare consultation were compared to those without early CVEs (control 1). To investigate the secondary outcomes, further comparisons were made among PWE experiencing each early CVE separately compared to PWE without experiencing early CVEs (control 1); as well as those without epilepsy matched for each CVE (control 2-6). All analyses were performed in the TriNetX online research platform which uses R's survival package v3.3.

Data Availability Statement and Ethical Approval

To gain access to the data in the TriNetX research network, requests are directed to TriNetX (https://live.trinetx.com) and a data sharing agreement is required. As a federated research network, studies using the TriNetX health research network do not need ethical approval as all data received and analyzed are fully anonymized.

Results

Baseline Characteristics and Short-Term Risk of CVEs in PWE

In total, 271,172 PWE were identified (Mean 50 ± 20 years; range 18-90 years; 52% female; 66% white, 19% Black or African American and 1% Asian). Overall, 38% had arterial hypertension, 17% diabetes mellitus, 9% chronic kidney disease, 13% ischemic heart disease and 8% HF at baseline.

Amongst PWE, the proportions experiencing CVEs within 30-days of first seizure-related healthcare consultation were 8.7% for the primary composite outcome, 0.9% for cardiac arrest, 2.8% for acute HF, 2.0% for ACS, 5.1% for AF, 0.7% for severe ventricular arrhythmias, and 1.7% for all-cause death (Table 1). In the repeat analysis excluding PWE with previous CVEs, the proportions experiencing incident CVEs within 30 days of a first seizure-related healthcare consultation were 2.5% for the composite outcome, 0.7% for cardiac arrest, 1.9% for acute HF, 0.9% for ACS, 2.3% for AF, and 0.6% for severe ventricular arrhythmias (Table 1).

TABLE 1. Thirty-days risk of early cardiovascular complications after epilepsy

	All population (n = 271,172)		Excluding patients with the outcome of interest prior to the time window		
	Events (n)	Proportion (%)	Patients (n)	Events (n)	Proportion (%)
Composite outcome	24,375	8.7	241,202	6,029	2.5
Cardiac arrest	2400	0.9	276,278	888	0.7
Acute HF	7909	2.8	270,169	5181	1.9
ACS	5557	2.0	264,219	2278	0.9
AF	14,175	5.1	258,453	2125	2.3
Severe ventricular arrhythmias	1861	0.7	274,882	755	0.6
All-cause death	4766	1.7	-	-	-

HF, Heart Failure; ACS, Acute Coronary Syndrome; AF, Atrial Fibrillation.

Given the wide age range found in PWE, we decided to further investigate the risk of CVEs within 30-days of a first seizure-related healthcare consultation, dividing the total population in 3 different age subgroups: (1) 18-39 years (n = 96,266; 35.5%), (2) 40-60 years (n = 84,877; 31.3%), and (3) 61-90 years (n = 90,029; 33.2%). In this sub-group analysis, risk of the composite outcome was 1.7% in the group aged 18-39 years, 5.8% in the group aged 18-39 years, and 19.5% in the group aged 60-90 years (Fig 1, Supplementary Table 3). For the primary outcome, each CVE risk showed a progressive increase with age, ranging between 0.4%-1.4% for cardiac arrest, 0.6%-6.5% for acute HF, 0.5%-4.2% for ACS, 0.4%-12.5% for AF, 0.2%-1.4% for severe ventricular arrhythmias and 0.4%-4.1% for all-cause death (Fig 1, Supplementary Table 3).

Long-Term Clinical Outcomes in Patients With Epilepsy and Early CVEs

PWE experiencing CVEs within 30 days of a first seizure-related healthcare consultation tended to be older and were mostly men. They also had a higher prevalence of cardiovascular risk factors and comorbidities than PWE not experiencing the 30-day CVE outcome (Table 2).

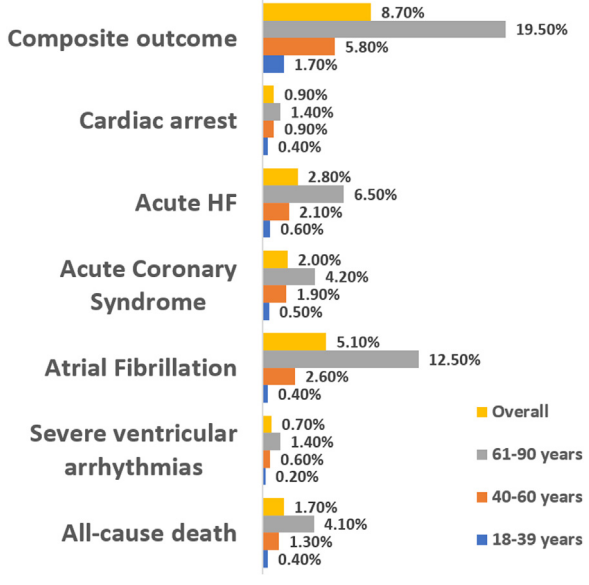

FIG 1. 30-days risk of early cardiovascular complications after epilepsy in different age ranges (Color version of figure is available online.)

TABLE 2. Baseline characteristics of patients with epilepsy with or without early CVEs before and after propensity score matching

	Before propensity score match			After propensity score match		
	Epilepsy with CVEs n = 15,120	**Epilepsy without CVEs n = 256,052**	**Std. diff.**	**Epilepsy with CVEs n = 15,120**	**Epilepsy without CVEs n = 15,120**	**Std. diff.**
Age, years (±SD)	62.5 ± 17.3	48.7 ± 19.3	0.759	62.5 ± 17.2	63.7 ± 16.9	0.086
Female	7453 (49.3)	133,038 (51.9)	0.054	7453 (49.3)	7413 (48.9)	0.022
White	9900 (65.4)	168,941 (66.4)	0.011	16,511 (65.5)	16,445 (65.2)	0.004
Black or African American	3409 (22.5)	46,318 (18.1)	0.111	3409 (22.5)	3427 (22.7)	0.018
Arterial hypertension	9343 (61.8)	68,644 (26.8)	0.751	9343 (61.8)	9409 (62.2)	0.009
Diabetes mellitus	4735 (31.3)	29,843 (11.7)	0.493	4735 (31.3)	4528 (29.9)	0.024
Chronic kidney disease	3407 (22.5)	14,521 (5.7)	0.499	3407 (22.5)	3009 (20.0)	0.066
Pulmonary heart disease	1599 (10.6)	6943 (2.7)	0.319	1599 (10.6)	1332 (8.8)	0.045
Chronic ischemic heart disease	3668 (24.2)	16,356 (6.4)	0.512	3668 (24.2)	3394 (22.4)	0.027
Chronic heart failure	3000 (19.9)	10,142 (4.0)	0.506	3000 (19.9)	2524 (16.7)	0.026
Cerebrovascular disease	5453 (36.0)	38,556 (15.1)	0.495	5453 (36.0)	5362 (35.4)	0.012
Cardiovascular procedures*	8863 (58.7)	73,797 (28.9)	0.629	8863 (58.7)	8940 (59.3)	0.008
Lipid-lowering drugs	6201 (41.0)	50,084 (19.6)	0.480	6201 (41.0)	6078 (40.2)	0.001
Beta-blockers	7199 (47.6)	52,919 (20.7)	0.592	7199 (47.6)	7031 (46.5)	0.008
Diuretics	6037 (39.9)	42,840 (16.7)	0.532	6037 (39.9)	5927 (39.2)	0.020
Antiarrhythmics	7588 (50.2)	70,963 (27.7)	0.473	7588 (50.2)	7457 (49.3)	0.006
Calcium channel blockers	4936 (32.6)	34,950 (13.6)	0.462	4936 (32.6)	4894 (32.3)	0.009
ACE inhibitors	3849 (25.4)	29,727 (11.6)	0.362	3849 (25.4)	3803 (25.1)	0.012
Angiotensin II inhibitors	2157 (14.3)	15,478 (6.0)	0.275	2157 (14.3)	2045 (13.5)	<0.001

CVEs, Cardiovascular Events.

*Including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures.

After 1:1 PSM, 15,120 patients were included in each group and no significate difference was found between the 2 groups.

On Cox regression analysis, PWE experiencing CVEs within 30 days of a first seizure-related healthcare consultation demonstrated significantly increased hazards for the composite primary outcome (HR 2.44, 95% 2.37-2.51), ischemic heart disease (HR 3.23, 95% CI 3.10-3.36), stroke (HR 1.56, 95% CI 1.48-1.64), hospitalization (HR 2.03, 95% CI 1.97-2.10) and all-cause death (HR 2.75, 95% CI 2.61-2.89), when compared to PWE not experiencing the 30-day CVE outcome (Table 3, Fig 2).

Type of CVE and Long-Term Risk of Adverse Events

The numbers of PWE in each secondary outcome subgroup after 1:1 PSM were as follows: 4068 for cardiac arrest, 4262 for acute HF, 8406 for ACS, 11,870 for AF and 3331 for severe ventricular arrhythmias. The highest 5-year risk of the composite outcome was associated with PWE experiencing cardiac arrest within 30 days of a first seizure-related healthcare consultation (HR 2.72, 95% CI 2.58-2.89), and in those experiencing ACS (HR 2.35, 95% CI 2.67-2.44) (Table 4). The highest risks of ischemic heart disease (HR 3.47, 95% CI 3.30-3.65) and stroke (HR 1.25, 95% CI 1.18-1.34) were found in PWE experiencing ACS, whereas the highest risks of hospitalization (HR 2.09, 95% CI 1.95-2.24) were found in PWE experiencing cardiac arrest: and the mortality risk was almost 6-fold increased in this subgroup (HR 5.77, 95% CI 5.27-6.32) (Table 4).

When determining the 5-year risk of adverse events in PWE experiencing CVEs within 30 days of a first seizure-related healthcare consultation

TABLE 3. Five-year risk of ischemic heart disease, stroke, hospitalization, and all-cause death in patients with epilepsy and early CVEs compared to those without early CVEs, after propensity score matching

	Patients with epilepsy and early CVEs (n = 15,120)		
	Events (n)	HR	95%CI
Composite outcome	12,218	2.44	2.37−2.51
Ischemic heart disease	4341	3.23	3.10−3.36
Stroke	3429	1.56	1.48−1.64
Hospitalization	8557	2.03	1.97−2.10
All-cause death	4130	2.75	2.61−2.89

CVEs, Cardiovascular Events; HR, Hazard Ratio; CI, Confidence Interval.

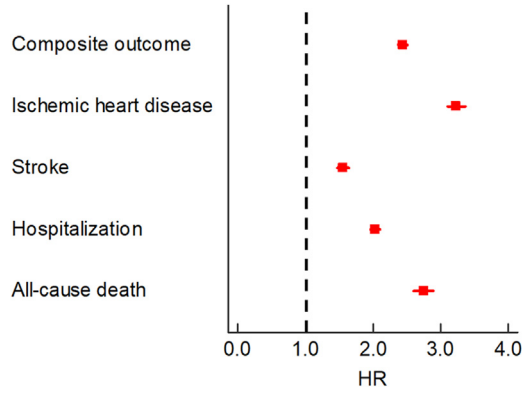

FIG 2. 5-year risk of adverse events in patients with epilepsy and early cardiovascular complications compared to patients with epilepsy without early cardiovascular complications (Color version of figure is available online.)

to controls (people without epilepsy matched for each CVE), the numbers of people in each group were: 4067 for cardiac arrest, 4266 for acute HF, 8408 for ACS, 11,878 for AF and 3279 for severe ventricular arrhythmia. The 5-year risk of the primary composite outcome in PWE experiencing CVEs within 30 days of a first seizure-related healthcare consultation was higher than in the matched controls (Table 5). The 5-year HR of adverse events was 1.53 (95% CI 1.45-1.57) for cardiac arrest, 1.30 (95% CI 1.24-1.37) for acute HF, 1.32 (95% CI 1.28-1.36) for ACS, 1.83 (95% CI 1.77-1.90) for AF, and 1.38 (95% CI 1.30-1.46) for severe ventricular arrhythmia.

Discussion

In this large multicenter observational study exploring the burden of early and late CVEs in PWE, we show that overall, nearly 9% of PWE experience a CVE within 30-days after a suspected seizure ranging between 1.7% in PWE aged 18-39 years to 19.5% in those aged more than 60 years. Second, the PWE experiencing early CVEs after seizures suffer a higher prevalence of long-term cardiovascular events at 5 years, including ischemic heart disease and stroke. Third, PWE experiencing early CVEs after seizures are at increased long-term risk of hospitalization and death. Indeed, the 5-year risk of adverse events in PWE experiencing early CVEs after a seizure is much higher than in people experiencing CVEs but who do not have epilepsy.

Our study adds to a growing body of evidence that CVEs are a major concern for PWE.[16,17] Hence, an integrated neurology and cardiovascular

TABLE 4. Five-year risk of ischemic heart disease, stroke, hospitalization, and all-cause death for each early CVEs in patients with epilepsy

	Epilepsy and Cardiac arrest (n = 4068)		Epilepsy and acute HF (n = 4262)		Epilepsy and ACS (n = 8406)		Epilepsy and AF (n = 11,870)		Epilepsy and ventricular arrhythmia (n = 3331)	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Composite outcome	2.72	2.58–2.89	2.12	2.02–2.23	2.35	2.67–2.44	1.81	1.75–1.87	2.18	2.05–2.31
Ischemic heart disease	1.73	1.58–1.90	2.28	2.14–2.44	3.47	3.30–3.65	1.87	1.78–1.96	2.18	2.00–2.37
Stroke	0.90	0.80–1.01	1.00	0.92–1.09	1.25	1.18–1.34	1.19	1.12–1.26	1.14	1.02–1.27
Hospitalization	2.09	1.95–2.24	1.98	1.86–2.11	1.90	1.82–1.99	1.73	1.67–1.80	1.92	1.78–2.06
All-cause death	5.77	5.27–6.32	2.22	2.04–2.42	1.92	1.80–2.05	1.86	1.76–1.96	2.55	2.31–2.81

HR, Hazard Ratio; CI. Confidence Interval; HF, Heart Failure; ACS, Acute Coronary Syndrome; AF, Atrial Fibrillation.

TABLE 5. Five-year risk of ischemic heart disease, stroke, hospitalization and death in patients with epilepsy and early CVEs compared to patients matched for CVE without epilepsy

	Epilepsy and Cardiac arrest (n = 4067)		Epilepsy and acute HF (n = 4266)		Epilepsy and ACS (n = 8408)		Epilepsy and AF (n = 11,878)		Epilepsy and ventricular arrhythmia (n = 3279)	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Composite outcome	1.41	1.34–1.50	1.24	1.19–1.31	1.32	1.28–1.36	1.65	1.60–1.70	1.26	1.20–1.34
Ischemic heart disease	0.95	0.86–1.05	1.02	0.96–1.08	0.95	0.91–0.99	1.11	1.07–1.16	0.78	0.72–0.84
Stroke	1.57	1.33–1.85	1.67	1.50–1.85	1.67	1.50–1.85	1.88	1.76–2.01	1.94	1.70–2.22
Hospitalization	1.93	1.79–2.01	1.06	1.01–1.18	1.27	1.20–1.34	1.90	1.82–1.98	1.44	1.34–1.54
All-cause death	1.27	1.19–1.37	1.46	1.35–1.57	1.59	1.50–1.70	1.72	1.63–1.81	1.40	1.29–1.53

HR, Hazard Ratio; CI, Confidence Interval; HF, Heart Failure; ACS, Acute Coronary Syndrome; AF, Atrial Fibrillation.

clinical service may be useful to help avert risks. For example, seizures may be a symptom of more severe vascular disease in someone known to have vascular disease or may be a presentation of hitherto occult vascular disease, requiring risk factor management that is not currently routine practice in epilepsy services or mentioned in epilepsy guidelines.

The higher prevalence of long-term cardiovascular comorbidity at 5 years including ischemic heart disease and stroke have been shown in Denmark, Taiwan, the UK, and the US.[2,3,17-19] PWE experiencing CVEs soon after seizures are at increased long-term risk of hospitalization and death compared to PWE who do not experience these early CVEs. These observations echo other findings from smaller cohorts in the US and in European countries.[20,21]

As PWE are at substantially increased risk of death, the addition of cardiac comorbidity appears to interact with and heighten that risk.[22] This makes cardiovascular co-morbidity a suitable target for treatment to help avoid increased epilepsy-related mortality. This may include more tightly controlling blood pressure, heart rate in AF, stroke secondary prevention, and regular or joint cardiology-neurology clinics, which are strategies that are currently not commonplace for PWE. Such an integrated care approach has been increasingly advocated for in the management of various chronic long-term conditions.[23,24] Indeed, cardiovascular morbidity should not be disregarded when prescribing anti-seizure medications, particularly as long-term use of enzyme inducing antiseizure medications contributes to cardiovascular disease.[25]

Finally, the 5-year risk of adverse events in PWE experiencing early CVEs after a seizure is higher than in people experiencing CVEs but who do not have epilepsy, suggesting seizures play an important role in the worsening outcomes in people experiencing CVEs. Hence, there is likely to be a heightened importance of achieving seizure control for PWE experiencing CVEs, which will require services configured to do so. By contrast, neurology services have focused on children and younger adults, historically, as have clinical trials assessing antiseizure medications. The interplay found in our study between epilepsy and CVEs reinforces the hypothesis of a synergic effect between myocardial and neuronal damage in increasing the long-term risk of adverse events and adds further evidence to the likely existence of an "Epilepsy-Heart Syndrome."

Strengths and Limitations

This is the first study that provides prognostic information about the short- and long-term risk of CVEs in a population of more than 270,000

PWE. Nonetheless, there are several limitations to consider. Health care organization EMR data are subject to entry errors and data gaps, and some diagnoses may be underreported, while outcomes which occurred outside the studies network may have not been captured. Our analysis assumed that each G40-coded activity reported in the TriNetX platform correlated with a seizure, seizure-related emergency department or hospital admission relating to a seizure. This is because these are the most common healthcare areas in which such diagnostic coded activity is generated within TriNetX. Establishing more granular information about exactly when a seizure occurred is not possible within this administrative dataset. Furthermore, despite the analysis having been matched for the patients' age at the index events and our investigating the risk of early CVE in 3 different age groups, no information was available regarding the date of epilepsy onset. This makes it impossible to match the survival analysis for the disease duration. Other important limitations were the lack of matching for antiseizures medications, epilepsy etiology, socioeconomic status, undiagnosed atherosclerotic disease, and geographical location, which are factors that may have confounded our results.

Conclusion

Large proportions of PWE with active disease experience CVEs. The onset of early CVEs is associated with a poor long-term outcomes including ischemic heart diseases, hospitalization, and all-cause death. This adds evidence to the theoretical existence of an 'Epilepsy-Heart Syndrome'.

Acknowledgments

Anthony G. Marson is a National Institute for Health Research (NIHR) Senior Investigator and also part funded by NIHR ARC Northwest Coast. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. Gashirai Mbizvo is supported by an NIHR Clinical Lectureship (CL-2022-07-002).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gregory Y.H. Lip is a consultant and speaker for BMS/Pfizer, Boehringer

Ingelheim and Daiichi-Sankyo. No fees are received personally. All other authors report no disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2023.101868.

REFERENCES

1. Brigo F, Lochner P, Nardone R, Manganotti P, Lattanzi S. Increased risk of stroke and myocardial infarction in patients with epilepsy: A systematic review of population-based cohort studies. *Epilepsy Behav* 2020;104:106307.
2. Wannamaker BB, Wilson DA, Malek AM, Selassie AW. Stroke after adult-onset epilepsy: A population-based retrospective cohort study. *Epilepsy Behav* 2015;43:93–9.
3. Hsu SPC, Yeh CC, Chou YC, et al. Stroke risk and outcomes in epilepsy patients: Two retrospective cohort studies based on National Health Insurance in Taiwan. *Atherosclerosis* 2019;280:147–54.
4. Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: A total population study. *Lancet* 2013;382:1646–54.
5. Lee-Lane E, Torabi F, Lacey A, et al. Epilepsy, antiepileptic drugs, and the risk of major cardiovascular events. *Epilepsia* 2021;62:1604–16.
6. Vivanco-Hidalgo RM, Gomez A, Moreira A, Diez L, Elosua R, Roquer J. Prevalence of cardiovascular risk factors in people with epilepsy. *Brain Behav* 2017;7:e00618.
7. Elliott JO, Lu B, Moore JL, McAuley JW, Long L. Exercise, diet, health behaviors, and risk factors among persons with epilepsy based on the California Health Interview Survey, 2005. *Epilepsy Behav* 2008;13:307–15.
8. Yamamoto Y, Terada K, Takahashi Y, Imai K, Kagawa Y, Inoue Y. Influence of antiepileptic drugs on serum lipid levels in adult epilepsy patients. *Epilepsy Res* 2016;127:101–6.
9. Voudris KA, Attilakos A, Katsarou E, et al. Early and persistent increase in serum lipoprotein (a) concentrations in epileptic children treated with carbamazepine and sodium valproate monotherapy. *Epilepsy Res* 2006;70:211–7.
10. Nikolaos T, Stylianos G, Chryssoula N, et al. The effect of long-term antiepileptic treatment on serum cholesterol (TC, HDL, LDL) and triglyceride levels in adult epileptic patients on monotherapy. *Med Sci Monit* 2004;10:MT50–2.
11. Arntz R, Rutten-Jacobs L, Maaijwee N, et al. Post-stroke epilepsy in young adults: A long-term follow-up study. *PLoS One* 2013;8:e55498.
12. Sander JW, Hart YM, Johnson AL, Shorvon SD. National general practice study of epilepsy: Newly diagnosed epileptic seizures in a general population. *Lancet* 1990;336:1267–71.
13. Thijs RD, Ryvlin P, Surges R. Autonomic manifestations of epilepsy: Emerging pathways to sudden death? *Nat Rev Neurol* 2021;17:774–88.

14. Verrier RL, Pang TD, Nearing BD, Schachter SC. The epileptic heart: Concept and clinical evidence. *Epilepsy Behav* 2020;105:106946.
15. Mbizvo GK, Derry C, Davenport R. Ictal asystole: a diagnostic and management conundrum. *J R Coll Physicians Edinb* 2019;49:128–31.
16. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. *J Neurol Neurosurg Psychiatry* 2016;87:69–74.
17. Rossi KC, Gursky JM, Pang TD, Dhamoon MS. Seizures and status epilepticus may be risk factor for cardiac arrhythmia or cardiac arrest across multiple time frames. *Epilepsy Behav* 2021;120:107998.
18. Mason ST, Corcoran ME. Catecholamines and convulsions. *Brain Res* 1979;170: 497–507.
19. Desai R, Rupareliya C, Patel U, et al. Burden of Arrhythmias in epilepsy patients: A nationwide inpatient analysis of 1.4 million hospitalizations in the United States. *Cureus* 2017;9:e1550.
20. Costagliola G, Orsini A, Coll M, Brugada R, Parisi P, Striano P. The brain-heart interaction in epilepsy: Implications for diagnosis, therapy, and SUDEP prevention. *Ann Clin Transl Neurol* 2021;8:1557–68.
21. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nat Rev Neurol* 2011;7:31–40.
22. Mbizvo GK, Bennett K, Simpson CR, Duncan SE, Chin RFM. Epilepsy-related and other causes of mortality in people with epilepsy: A systematic review of systematic reviews. *Epilepsy Res* 2019;157:106192.
23. Lip GYH, Ntaios G. "Novel clinical concepts in thrombosis": Integrated care for stroke management-easy as ABC. *Thromb Haemost* 2022;122:316–9.
24. Field M, Kuduvalli M, Torella F, McKay V, Khalatbari A, Lip GYH. Integrated care systems and the aortovascular hub. *Thromb Haemost* 2022;122:177–80.
25. Josephson CB, Wiebe S, Delgado-Garcia G, et al. Association of enzyme-inducing antiseizure drug use with long-term cardiovascular disease. *JAMA Neurol* 2021; 78:1367–74.