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

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**Abstract**

**Background**: The risks of cardiovascular events(CVEs) in people with epilepsy(PWE) are not well understood.

**Objectives**: To establish the short- and long-term burden of CVEs in PWE.

**Methods**: Electronic health records from a global federated health research network(TriNetX) were used to establish a cohort of PWE. Primary outcomes were: i) the proportion of people experiencing a composite 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 seizure; and ii) 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).

**Results**: 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).

**Conclusions**: 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’.

**Keywords:** epilepsy, cardiovascular events, death.

**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.

**ABBREVIATIONS**

CVEs: Cardiovascular Events

ACS: Acute Coronary Syndrome

PWE: People With Epilepsy

CAN: Central Autonomic Network

HF: Heart Failure

EMRs: Electronic Medical Records

AF: Atrial Fibrillation

PSM: Propensity Score Matching

Std diff.: Standardized mean differences

**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. In this context, should be also considered that epilepsy may 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]) control cardiovascular functions via sympathetic and parasympathetic outflow. After an acute neurological injury, the damaged connections induce local and systemic inflammatory response, potentially causing myocardial necrosis, microvascular dysfunction, coronary ischemia, heart failure (HF) and arrhythmogenesis or asystole13, 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 (e.g. 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 asystole associated with convulsive seizures can carries a higher risk of fatality interfering with the postictal come resumption of ventilation and leading to sudden unexpected death 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 complicationsin 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 (U.S.). 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 the 28th of December 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), 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 (i.e., a G40-coded event) amongst PWE were: i) 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 ii) 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 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: i) PWE not experiencing the 30-day CVE outcome, and ii) patients without epilepsy with each type of CVE.

 All statistical analyses were performed on the TriNetX online research platform. 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 platform which uses R’s survival package v3.3.

*Data availability statement & 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**).

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 three different age subgroups: i) 18-39 years (n=96,266; 35.5%), ii) 40-60 years (n=84,877; 31.3%), and iii) 61-90 years (n=90,029; 33.2%). On this sub-group analysis, the risk of composite outcome was 1.7% in the 18-39 years group, 5.8% in the 40-60 years group and 19.5% in the 60-90 years group (**Figure 1, Supplementary Table 3**). As well as for the primary outcome, each CVE risk showed a progressively increase with the age ranging between 0.4% to 1.4% for cardiac arrest, 0.6% to 6.5% for acute HF, 0.5% to 4.2% for ACS, 0.4% to 12.5% for AF, 0.2% to 1.4% for severe ventricular arrhythmias and 0.4% to 4.1% for all-cause death (**Figure 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**). After 1:1 PSM, 15,120 patients were included in each group and no significative difference was found between the two 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, Figure 2**).

*Type of CVE and long-term risk of adverse events.*

The numbers of PWE each secondary outcome subgroup after 1:1 PSM were as follows: 4,068 for cardiac arrest, 4,262 for acute HF, 8,406 for ACS, 11,870 for AF and 3,331 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 to controls (people without epilepsy matched for each CVE), the numbers of people in each group were: 4,067 for cardiac arrest, 4,266 for acute HF, 8,408 for ACS, 11,878 for AF and 3,279 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 with 18-39 years to 19.5% in those with 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 suffer 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 clinical service may be useful to help avert risks. For example, seizures may be a symptom of more severe vascular disease in someone known 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.

PWE are at substantially increased risk of death, and the addition of cardiac comorbidity appears to interact with and heighten that risk 22. This makes cardiovascular comorbidities a suitable target for treatment to help avoid increased epilepsy-related mortality, such as more tightly controlling blood pressure, heart rate in AF, stroke secondary prevention, and regular or joint cardiology-neurology follow-up, which is currently not commonplace for PWE. Such an integrated care approach has been increasingly advocated for the management of various chronic long-term conditions 23, 24. Indeed, cardiovascular morbidity should not be disregarding 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, the likely importance of achieving seizure control for PWE experiencing CVEs, which will require services configured to do so, where in contrast neurology services historically have focussed on children and younger adults, as have clinical trials assessing anti-seizure 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 further adds to the 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 was matched for the patients’ age at the index events and we investigated the risk of early CVE in three different age groups, no information was available regarding the date of epilepsy onset making 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, that could 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 outcome including ischemic heart diseases, hospitalization, and all-cause death, suggesting the existence of an ‘epilepsy-heart syndrome’.

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Table 1.30-days risk of early cardiovascular complications after epilepsy.

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| --- | --- | --- |
|  | 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 | 2,400 | 0.9 | 276,278 | 888 | 0.7 |
| Acute HF | 7,909 | 2.8 | 270,169 | 5,181 | 1.9 |
| ACS | 5,557 | 2.0 | 264,219 | 2,278 | 0.9 |
| AF | 14,175 | 5.1 | 258,453 | 2,125 | 2.3 |
| Severe ventricular arrhythmias | 1,861 | 0.7 | 274,882 | 755 | 0.6 |
| All-cause death | 4,766 | 1.7 | - | - | - |

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

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

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| --- | --- | --- |
|  | Before propensity score match | After propensity score match |
|  | Epilepsy with CVEsn=15,120 | Epilepsy without CVEsn=256,052 | Std. diff. | Epilepsy with CVEsn=15,120 | Epilepsy without CVEsn=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 | 7,453 (49.3) | 133,038 (51.9) | 0.054 | 7,453 (49.3) | 7,413 (48.9) | 0.022 |
| White | 9,900 (65.4) | 168,941 (66.4) | 0.011 | 16,511 (65.5) | 16,445 (65.2) | 0.004 |
| Black or African American | 3,409 (22.5) | 46,318 (18.1) | 0.111 | 3,409 (22.5) | 3,427 (22.7) | 0.018 |
| Arterial hypertension | 9,343 (61.8) | 68,644 (26.8) | 0.751 | 9,343 (61.8) | 9,409 (62.2) | 0.009 |
| Diabetes mellitus | 4,735 (31.3) | 29,843 (11.7) | 0.493 | 4,735 (31.3) | 4,528 (29.9) | 0.024 |
| Chronic kidney disease | 3,407 (22.5) | 14,521 (5.7) | 0.499 | 3,407 (22.5) | 3,009 (20.0) | 0.066 |
| Pulmonary heart disease | 1,599 (10.6) | 6,943 (2.7) | 0.319 | 1,599 (10.6) | 1,332 (8.8) | 0.045 |
| Chronic ischemic heart disease | 3,668 (24.2) | 16,356 (6.4) | 0.512 | 3,668 (24.2) | 3,394 (22.4) | 0.027 |
| Chronic heart failure | 3,000 (19.9) | 10,142 (4.0) | 0.506 | 3,000 (19.9) | 2,524 (16.7) | 0.026 |
| Cerebrovascular disease | 5,453 (36.0) | 38,556 (15.1) | 0.495 | 5,453 (36.0) | 5,362 (35.4) | 0.012 |
| Cardiovascular procedures\* | 8,863 (58.7) | 73,797 (28.9) | 0.629 | 8,863 (58.7) | 8,940 (59.3) | 0.008 |
| Lipid-lowering drugs | 6,201 (41.0) | 50,084 (19.6) | 0.480 | 6,201 (41.0) | 6,078 (40.2) | 0.001 |
| Beta-blockers | 7,199 (47.6) | 52,919 (20.7) | 0.592 | 7,199 (47.6) | 7,031 (46.5) | 0.008 |
| Diuretics | 6,037 (39.9) | 42,840 (16.7) | 0.532 | 6,037 (39.9) | 5,927 (39.2) | 0.020 |
| Antiarrhythmics | 7,588 (50.2) | 70,963 (27.7) | 0.473 | 7,588 (50.2) | 7,457 (49.3) | 0.006 |
| Calcium channel blockers | 4,936 (32.6) | 34,950 (13.6) | 0.462 | 4,936 (32.6) | 4,894 (32.3) | 0.009 |
| ACE inhibitors | 3,849 (25.4) | 29,727 (11.6) | 0.362 | 3,849 (25.4) | 3,803 (25.1) | 0.012 |
| Angiotensin II inhibitors | 2157 (14.3) | 15478 (6.0) | 0.275 | 2157 (14.3) | 2045 (13.5) | <0.001 |

 |

CVEs Cardiovascular Events; **\*** Including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures.

Table 3.5-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 | 4,341 | 3.23 | 3.10-3.36 |
| Stroke | 3,429 | 1.56 | 1.48-1.64 |
| Hospitalization | 8,557 | 2.03 | 1.97-2.10 |
| All-cause death | 4,130 | 2.75 | 2.61-2.89 |

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

Table 4.5-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=4,068) | Epilepsy and acute HF (n=4,262) | Epilepsy and ACS (n=8,406) | Epilepsy and AF (n=11,870) | Epilepsy and ventricular arrhythmia (n=3,331) |
|  | 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 5.5-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=4,067) | Epilepsy and acute HF (n=4,266) | Epilepsy and ACS (n=8,408) | Epilepsy and AF (n=11,878) | Epilepsy and ventricular arrhythmia (n=3,279) |
|  | 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.

**Figure legends:**

**Figure 1.** 30-days risk of early cardiovascular complications after epilepsy in different age ranges.

**Figure 2.** 5-year risk of adverse events in patients with epilepsy and early cardiovascular complications compared to patients with epilepsy without early cardiovascular complications.