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Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Epilepsy, antiepileptic drugs, and the risk of major cardiovascular events

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Summary

Objective: This study was undertaken to determine whether epilepsy and antiepileptic drugs (including enzyme-inducing and non-enzyme-inducing drugs) are associated with major cardiovascular events using population-level, routinely collected data.

Methods: Using anonymized, routinely collected, health care data in Wales, UK, we performed a retrospective matched cohort study (2003–2017) of adults with epilepsy prescribed an antiepileptic drug. Controls were matched with replacement on age, gender, deprivation quintile, and year of entry into the study. Participants were followed to the end of the study for the occurrence of a major cardiovascular event, and survival models were constructed to compare the time to a major cardiovascular event (cardiac arrest, myocardial infarction, stroke, ischemic heart disease, clinically significant arrhythmia, thromboembolism, onset of heart failure, or a cardiovascular death) for individuals in the case group versus the control group.

Results: There were 10 241 cases (mean age = 49.6 years, 52.2% male, mean follow-up = 6.1 years) matched to 35 145 controls. A total of 3180 (31.1%) cases received enzyme-inducing antiepileptic drugs, and 7061 (68.9%) received non-enzyme-inducing antiepileptic drugs. Cases had an increased risk of experiencing a major cardiovascular event compared to controls (adjusted hazard ratio = 1.58, 95% confidence interval [CI] = 1.51–1.63, $p < .001$). There was no notable difference in major cardiovascular events between those treated with enzyme-inducing antiepileptic drugs and those treated with non-enzyme-inducing antiepileptic drugs (adjusted hazard ratio = .95, 95% CI = .86–1.05, $p = .300$).

Significance: Individuals with epilepsy prescribed antiepileptic drugs are at an increased risk of major cardiovascular events compared with population controls. Being prescribed an enzyme-inducing antiepileptic drug is not associated with a greater risk of a major cardiovascular event compared to treatment with other antiepileptic drugs. Our data emphasize the importance of cardiovascular risk management in the clinical care of people with epilepsy.

KEYWORDS
cardiovascular risk, enzyme-inducing antiepileptic drugs

1 | INTRODUCTION

Epilepsy is a common neurological condition, and individuals with epilepsy have higher mortality rates than the general population.[1,2] Although part of this increased risk may be explained by comorbid conditions or lifestyle factors, cardiovascular events associated with epilepsy or antiepileptic drugs (AEDs) may also contribute.

For most people with epilepsy, AEDs are the mainstay of treatment. Previous studies have suggested a link between AEDs and an increased risk of cardiovascular events, such as stroke, myocardial infarction, and arrhythmia.[3–5] AEDs can be grouped into enzyme-inducing AEDs (EIAEDs; e.g., phenytoin, phenobarbital, and carbamazepine) and non-enzyme-inducing AEDs (NEIAEDs), based on their action on the hepatic enzyme system.[6] Older AEDs, which are mainly enzyme inducers, may be associated with more adverse effects and may alter metabolic pathways related to vascular risk.[7–9] EIAEDs are associated with elevated levels of total cholesterol and low-density lipoprotein cholesterol due to effects on enzymes involved in cholesterol synthesis.[7–13] Other vascular risk markers may be affected by AEDs, including homocysteine and C-reactive protein.[14,15]

Despite the evidence linking AEDs to lipid abnormalities, there is a lack of evidence of their effect on cardiovascular events. AEDs are long-term treatments, and it is therefore important to fully understand any potential side effects.

This study aimed to evaluate whether individuals with epilepsy who are taking AEDs are at greater risk of experiencing a major cardiovascular event than individuals without epilepsy. The study also examined whether the risk of clinically relevant cardiovascular outcomes differed in those treated with EIAEDs compared to NEIAEDs.

Key Points

- We studied 10 241 people with epilepsy who were prescribed antiepileptic drugs and 35 145 matched controls
- There was an increased risk of major cardiovascular events in the people with epilepsy
- There did not seem to be a difference when comparing enzyme-inducing and non-enzyme-inducing antiepileptic drugs
- Cardiovascular risk management is important in people with epilepsy

2 | MATERIALS AND METHODS

2.1 | Data source

The study used data within the Secure Anonymised Information Linkage (SAIL) databank, which contains anonymized, routinely collected electronic health record (EHR) data from secondary care (hospitals; 100% population coverage) and primary care general practices (around 80% population coverage) in Wales.[16,17] The following SAIL data sources were used: Annual District Death Extract (ADDE), Patient Episode Database for Wales (PEDW), Welsh Demographic Service Dataset, and Welsh Longitudinal General Practice (WLGP) data. Read codes are the clinical coding system used in UK primary care systems to record diagnoses, prescriptions, and symptoms.[18] Version 2 Read codes were used to identify cases of epilepsy, comorbidities, and prescriptions within WLGP data. International Classification of Diseases, 10th revision (ICD-10) codes were used to identify comorbidities, cardiovascular events in hospital data (PEDW), and causes of death in death certificate data (ADDE). Lists of Read and ICD-10 codes used are available from the corresponding author upon request.

2.2 | Study design

An algorithm that has previously been shown to be 84% sensitive and 98% specific was used to identify people with epilepsy using primary care records.[18] The algorithm requires cases to have an epilepsy diagnosis code as well as two subsequent AED prescription codes within a 6-month window.[18] A cohort of people with a diagnosis of epilepsy between January 1, 2003 and December 31, 2017 and a start date for their first AED was identified, and any previous cardiovascular disease was recorded at study entry. The study entry date was taken as the date of diagnosis of epilepsy. From this cohort, individuals were eligible for inclusion if they were at least 18 years of age at diagnosis, and had at least 6 months of available general practitioner (GP) data prior to and after their epilepsy diagnosis date. This criterion of 180 days of follow-up data meant that the latest epilepsy diagnosis date for inclusion in the study was June 30, 2017. We included

only adults in this study, due to major cardiovascular events being relatively uncommon in children.

Individuals were followed to the end of the study (December 31, 2017) for the occurrence of a major cardiovascular event. If patients died during the study period (other than for cardiovascular causes) or moved to GP practices with no SAIL data coverage, they were censored.

Individuals were classified as being in the EIAED group if they had at least two prescriptions of phenytoin, phenobarbital, carbamazepine, methylphenobarbital, or primidone.

A control cohort was obtained from all eligible individuals in Wales without a diagnosis of epilepsy and matched on a 1:4 ratio based on age (week of birth), gender, Welsh Index of Multiple Deprivation (WIMD) 2011 version quintile, and year of entry into the study to cases with epilepsy. To allow a sufficient number of possible matches on year of entry into the study, controls were returned into the matching pool after meeting matching criteria, allowing matching with replacement, where four controls were randomly selected from all possible matches for each case. Some individuals within the control cohort were therefore matched to more than one case.

2.3 | Assessment of a cardiovascular event

The primary outcome was the first occurrence of a major cardiovascular event, after a diagnosis of epilepsy, within the study window. This was defined as a cardiac arrest, myocardial infarction, stroke, ischemic heart disease, clinically significant arrhythmia (atrioventricular block, atrioventricular dissociation, ventricular tachycardia, paroxysmal atrioventricular tachycardia, paroxysmal atrial tachycardia, paroxysmal tachycardia, and partial atrioventricular block), thromboembolism, onset of heart failure, or a cardiovascular death. Cardiovascular events were obtained from primary care records, hospital data, and death certificates, using previously validated case definitions.[19] A cardiovascular death was defined as a death with any of the above events as the primary cause of death.

2.4 | Covariates

Baseline demographic and clinical characteristics were recorded to adjust the models for potential confounding factors. Deprivation was recorded using the WIMD 2011 version, which uses weighted scores from eight domains to form a score for small geographical areas or Lower Layer Super Output Areas (LSOAs). WIMD scores for each LSOA are then grouped into quintiles, with Quintile 1 being the most deprived and Quintile 5 being the least deprived. All variables were taken from the closest entry to the diagnosis date and identified with relevant diagnostic codes.

Smoking status was assigned following a previously validated method that uses primary care smoking status records to assign individuals into categories of smokers, ex-smokers, and never-smokers. The algorithm also addresses inconsistencies and changes in smoking status over an individual's lifetime by using the first and last recorded date of a code in each category.[20] Where the baseline smoking status was unavailable, the closest available recorded smoking status during the study period was used. If no smoking status was available, the participant was treated as a nonsmoker based on population estimates of smokers in Wales.[21]

Other conditions that may affect cardiovascular risk, such as diabetes, hypertension, and dyslipidemia were recorded, as well as previous cardiovascular events (cardiac arrest, myocardial infarction, stroke, ischemic heart disease, significant arrhythmia, thromboembolism, or onset of heart failure). Hypertension was recorded using diagnosis codes for hypertension, not prescriptions for antihypertensive agents. Medications prescribed within the study period that could affect cardiovascular risk (anticoagulants, antiplatelet drugs, and statins) were also recorded. Body mass index (BMI) was excluded from analysis due to high percentage of missing values (Table 1).

2.5 | Statistical analysis

Descriptive statistics were used to analyze the baseline demographic and clinical characteristics of the cohort and to compare the characteristics of people with and without epilepsy.

Unadjusted and adjusted survival (time-to-event) models for time to a cardiovascular event were constructed. Cox proportional hazard models were used for cardiovascular events for individuals in the case versus control groups. Survival models were adjusted for age, sex, WIMD quintile, smoking status, coprescription of antiplatelets, anticoagulants, or statins, and previous diagnoses of hypertension, dyslipidemia, diabetes, thromboembolism, significant arrhythmia, ischemic heart disease, atrial fibrillation, cardiac arrest, myocardial infarction, stroke, or heart failure. Time-to-event was defined as the time from the study entry date to either the first cardiovascular event or the time of censoring, whichever came first. Cases were censored on the first occurrence of moving to practices with no SAIL data coverage or noncardiovascular death. A logistic regression model was used to determine which of the baseline covariates had a significant impact on survival, with the occurrence or nonoccurrence of a cardiovascular event as the binary outcome variable. Adjusted Cox proportional hazard models were performed to calculate hazard ratios and estimate the risk of experiencing a cardiovascular event between treatment groups. A proportionality test was used to test for the proportional hazard assumption.

TABLE 1 Baseline characteristics of epilepsy (case) and matched control cohorts

Variable	Case, $n = 10\,241$, n (%)	Control, $n = 35\,145$, n (%)	p
Age			.451
18–64 years	7335 (71.6%)	25 111 (71.4%)	
65–74 years	1304 (12.7%)	4375 (12.4%)	
75+ years	1602 (15.6%)	5659 (16.1%)	
Sex			.640
Female	4897 (47.8%)	16 900 (48.1%)	
Male	5344 (52.2%)	18 245 (51.9%)	
BMI, kg/m^2			<.001
Underweight, BMI < 20	205 (2.0%)	571 (1.6%)	
Healthy weight, 20 ≤ BMI < 25	2147 (21.0%)	7337 (20.9%)	
Overweight, 25 ≤ BMI < 30	1301 (12.7%)	4395 (12.5%)	
Obese, BMI ≥ 30	724 (7.1%)	2139 (6.1%)	
Unknown	5864 (57.3%)	20 703 (58.9%)	
Smoking status			<.001
Nonsmoker	593 (5.8%)	2439 (6.9%)	
Ex-smoker	2318 (22.6%)	6455 (18.4%)	
Current smoker	3903 (38.1%)	11 373 (32.4%)	
Unknown status	3427 (33.5%)	14 878 (42.3%)	
WIMD deprivation quintile			.051
1, most deprived	2711 (26.5%)	9658 (27.5%)	
2	2118 (20.7%)	7139 (20.3%)	
3	2162 (21.1%)	7399 (21.1%)	
4	1623 (15.8%)	5223 (14.9%)	
5, least deprived	1627 (15.9%)	5726 (16.3%)	
Diabetes	473 (4.6%)	1224 (3.5%)	<.001
Hypertension	1291 (12.6%)	3825 (10.9%)	<.001
Dyslipidemia	320 (3.1%)	9221 (2.6%)	.007
Prior thromboembolism	5 (<.1%)	25 (.1%)	.579
Prior arrhythmia	16 (.2%)	65 (.2%)	.636
Prior cardiac arrest	8 (.1%)	16 (<.1%)	.309
Prior atrial fibrillation	152 (1.5%)	386 (1.1%)	.002
Prior ischemic heart disease	169 (1.7%)	507 (1.4%)	.139
Prior myocardial infarction	129 (1.3%)	391 (1.1%)	.239
Prior heart failure	73 (.7%)	190 (.5%)	.052
Prior stroke	383 (3.7%)	367 (1.0%)	<.001
Antiplatelet coprescription	3252 (31.8%)	7928 (22.6%)	<.001
Anticoagulant coprescription	898 (8.8%)	2521 (7.2%)	<.001
Statin coprescription	3489 (34.1%)	9925 (28.2%)	<.001

Note: Numbers in parentheses show value as a percentage of the entire cohort.

Abbreviations: BMI, body mass index; WIMD, Welsh Index of Multiple Deprivation.

Initial analyses compared differences between individuals in the epilepsy case and control groups. Cases were split into those treated with EIAEDs and NEIAEDs, and analysis was repeated to assess whether enzyme-inducing properties of AEDs affected the risk of experiencing a major cardiovascular event.

Propensity score estimates were used to predict the probability of being prescribed either an EIAED or NEIAED, and then data were matched based on the estimated propensity score to produce a balanced dataset using nearest neighbor matching. A paired *t*-test was performed on matched data to compare the two treatment groups. A *p*-value of <.05 was set to indicate statistical significance. R Version 3.5.3 was used for statistical analysis.[22] The R packages *survminer* and *survival* were used for survival analysis, and *ggplot2* to plot graphs.

2.6 | Ethics

Written informed consent was not required for this study, as it used anonymized routinely collected data. All studies using SAIL data need independent Information Governance Review Panel (IGRP) approval. This study obtained IGRP approval reference 0758. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort, case–control, and cross-sectional studies have been followed with respect to reporting observational research.[23]

2.7 | Data availability statement

Linked pseudonymized patient data were used in this study. Under SAIL governance, patient-level data are only available on the SAIL Databank safe research platform. All proposals to use SAIL data are subject to review by an independent IGRP. Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been approved, it is gained through a privacy-protecting safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL www.saildatabank.com/application-process. This study has been approved by the IGRP as project 0758.

3 | RESULTS

3.1 | Case and control cohorts

From a group of 26 351 individuals with a diagnosis of epilepsy, an epilepsy (case) cohort of 10 241 was obtained after applying inclusion criteria (Figure 1). Cases were matched to 40 964 controls, with 35 145 distinct people in the control cohort (5819 repeated matches).

The baseline clinical and demographic characteristics of the case and control cohorts can be seen in Table 1. In decreasing order, the most commonly prescribed NEIAEDs were sodium valproate, lamotrigine, levetiracetam, gabapentin, and pregabalin. Similarly, carbamazepine, phenytoin, primidone, and phenobarbital were the most commonly prescribed EIAEDs (Table S1). During a mean (±SD) of 6.05 (±4.31) years of overall follow-up (62 000 person-years), 2115 major cardiovascular events occurred in the case cohort

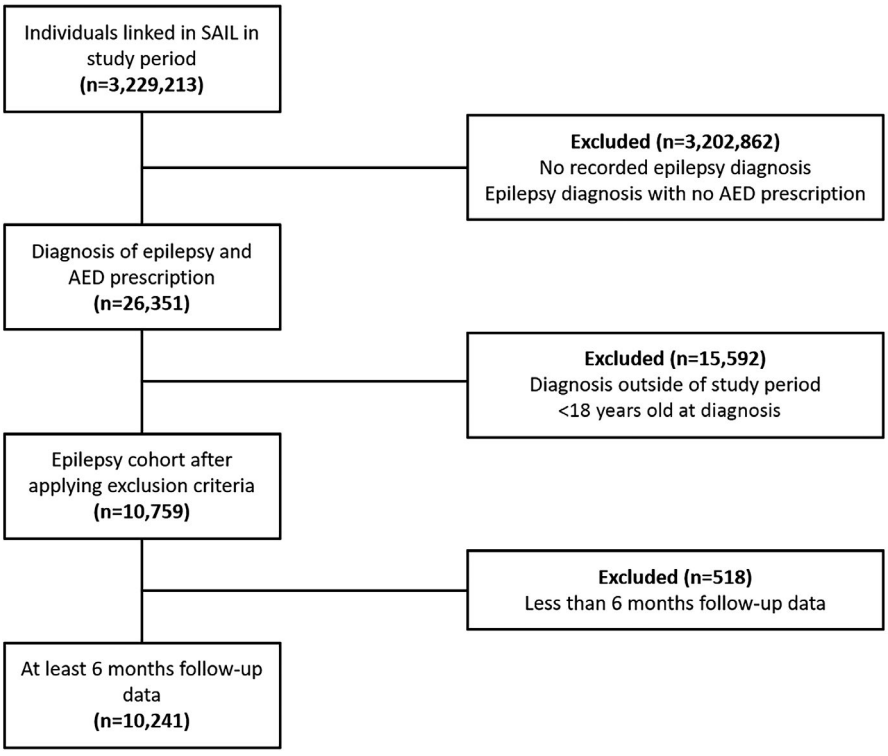

FIGURE 1 Flow diagram of cohort selection. AED, antiepileptic drug; SAIL, Secure Anonymised Information Linkage Databank

(3.41 events per 100 person-years). In the control cohort, 4457 events were observed during a mean of 7.15 (±4.39) years of follow-up (251 330 person-years; 1.77 events per 100 person-years).

3.2 | Survival analysis for case versus control cohorts

The unadjusted and adjusted survival (time-to-event) models for time to a cardiovascular event for individuals in the case versus control groups can be seen in Figure 2. This model adjusted for age, sex, WIMD quintile, smoking status, coprescription of antiplatelets, anticoagulants, or statins, and previous diagnoses of hypertension, dyslipidemia, diabetes, thromboembolism, significant arrhythmia, ischemic heart disease, atrial fibrillation, cardiac arrest, myocardial infarction, stroke, or heart failure. The unadjusted Cox proportional hazard ratio for cardiovascular events in the case cohort was 1.47 (95% confidence interval [CI] = 1.45–1.50, $p < .001$), and the adjusted hazard ratio was 1.53 (95% CI 1.50–1.55), $p < .001$. Adjusting additionally for the time-dependent covariates (antiplatelet and anticoagulant coprescription) gave a hazard ratio of 1.58 (95% CI = 1.51–1.63, $p < .001$; Cox proportional hazard analysis).

3.3 | Survival analysis for EIAED versus NEIAED cohorts

There were 3180 individuals in the EIAED group (31.1% of cases) and 7061 in the NEIAED group (68.9% of cases). Individuals were placed in the EIAED treatment group if they had at least two prescriptions of an EIAED. The baseline clinical and demographic characteristics are summarized in Table 2. During a mean (±SD) of 7.36 (± 4.47) years of overall follow-up (total of 21 666 person-years), 632 major cardiovascular events occurred in the EIAED group (2.92 events per 100 person-years). In the NEIAED cohort, 1483 events were observed during a mean of 5.53 (±4.13) years (total of 40 355 person-years; 3.67 events per 100 patient years).

The unadjusted and adjusted survival (time-to-event) models for cardiovascular events in the NEIAED versus the EIAED group can be seen in Figure 3. The model adjusted for age, sex, smoking status, total AED prescription time (the total length of time for which an individual was prescribed either EIAEDs or NEIAEDs), a coprescription of antiplatelets, anticoagulants, or statins, or a previous diagnosis of hypertension, dyslipidemia, diabetes, thromboembolism, significant arrhythmia, ischemic heart disease, atrial fibrillation, cardiac arrest, myocardial infarction, stroke, or heart failure. The unadjusted Cox proportional hazard ratio for cardiovascular events in the NEIAED group compared to the EIAED group was 1.12 (95% CI = 1.04–1.20, $p = .004$). The adjusted hazard ratio for cardiovascular events in the EIAED group compared to the NEIAED group was .95 (95% CI = .86–1.05, $p = .300$). There was no difference in cardiovascular events in the propensity-matched EIAED and NEIAD groups (point estimate = .019, 95% CI = .007–.044, $p = .151$).

4 | DISCUSSION

In this study, 10 241 people with epilepsy who were taking AEDs had a higher risk of major cardiovascular events than a matched control cohort (adjusted hazard ratio = 1.58, 95% CI = 1.51–1.63). There was no difference in the risk of cardiovascular events in people with epilepsy who were prescribed

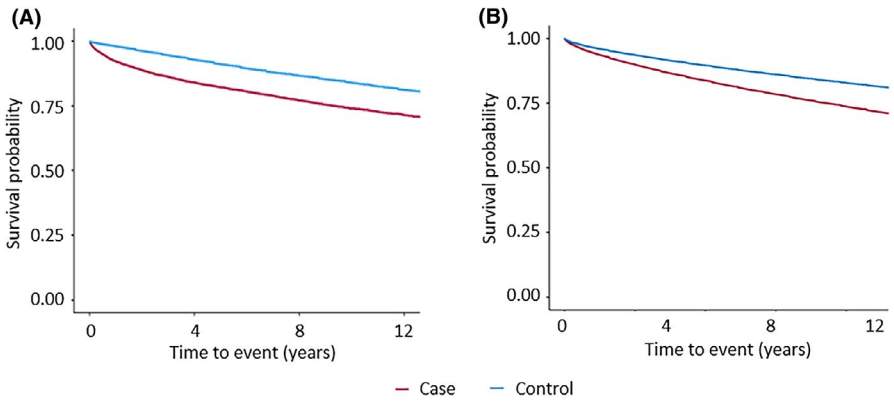

FIGURE 2 Unadjusted and adjusted time-to-event models for case versus control cohorts. (A) Unadjusted survival (time-to-event) models to compare the time to a cardiovascular event for individuals in the two treatment groups. Time-to-event is defined as the time from the index date (date of diagnosis/study start date) to either the first cardiovascular event or the time of censoring, whichever came first. (B) Survival model adjusted for age, sex, smoking status, a coprescription of antiplatelets, anticoagulants, or statins, or a previous diagnosis of hypertension, dyslipidemia, diabetes, thromboembolism, significant arrhythmia, ischemic heart disease, atrial fibrillation, cardiac arrest, myocardial infarction, stroke, or heart failure

TABLE 2 Baseline characteristics of EIAED and NEIAED treatment groups

Variable	EIAED, $n = 3180$, n (%)	NEIAED, $n = 7061$, n (%)	p
Age			<.001
18–64 years	2451 (77.1%)	4884 (69.2%)	
65–74 years	396 (12.5%)	908 (12.9%)	
75+ years	333 (10.5%)	1269 (18.0%)	
Sex			.303
Female	1496 (47.0%)	3401 (48.2%)	
Male	1684 (53.0%)	3660 (51.8%)	
BMI, kg/m^2			.072
Underweight, BMI < 20	71 (2.2%)	134 (1.9%)	
Healthy weight, 20 ≤ BMI < 25	711 (22.4%)	1436 (20.3%)	
Overweight, 25 ≤ BMI < 30	412 (13%)	889 (12.6%)	
Obese BMI ≥ 30	225 (7.1%)	499 (7.1%)	
Unknown	1761 (55.4%)	4103 (58.1%)	
Smoking status			.010
Nonsmoker	183 (5.8%)	410 (5.8%)	
Ex-smoker	658 (20.7%)	1660 (23.5%)	
Current smoker	1267 (39.8%)	2636 (37.3%)	
Unknown status	1072 (33.7%)	2355 (33.4%)	
WIMD deprivation quintile			.081
1, most deprived	830 (26.1%)	1881 (26.6%)	
2	711 (22.4%)	1407 (19.9%)	
3	664 (20.9%)	1498 (21.2%)	
4	488 (15.3%)	1145 (16.1%)	
5, least deprived	487 (15.3%)	1140 (16.1%)	
Diabetes	129 (4.1%)	344 (4.9%)	.077
Hypertension	351 (11.0%)	940 (13.3%)	.001
Dyslipidemia	109 (3.4%)	211 (3.0%)	.262
Prior thromboembolism	<5 (<.1%)	<5 (<.1%)	.360
Prior arrhythmia	<5 (<.1%)	14 (.2%)	.182
Prior cardiac arrest	<5 (<.1%)	6 (.1%)	1.000
Prior atrial fibrillation	39 (1.2%)	113 (1.6%)	.174
Prior ischemic heart disease	50 (1.6%)	119 (1.7%)	.740
Prior myocardial infarction	42 (1.3%)	87 (1.2%)	.782
Prior heart failure	21 (.7%)	52 (.7%)	.767
Prior stroke	134 (4.2%)	249 (3.5%)	.101
Antiplatelet coprescription	981 (30.8%)	2271 (32.2%)	.194
Anticoagulant coprescription	245 (7.7%)	653 (9.2%)	.012
Statin coprescription	1147 (36.1%)	2342 (33.2%)	.004

Note: Numbers in parentheses show value as a percentage of the entire cohort.

Abbreviations: BMI, body mass index; EIAED, enzyme-inducing antiepileptic drug; NEIAED, non-enzyme-inducing antiepileptic drug; WIMD, Welsh Index of Multiple Deprivation.

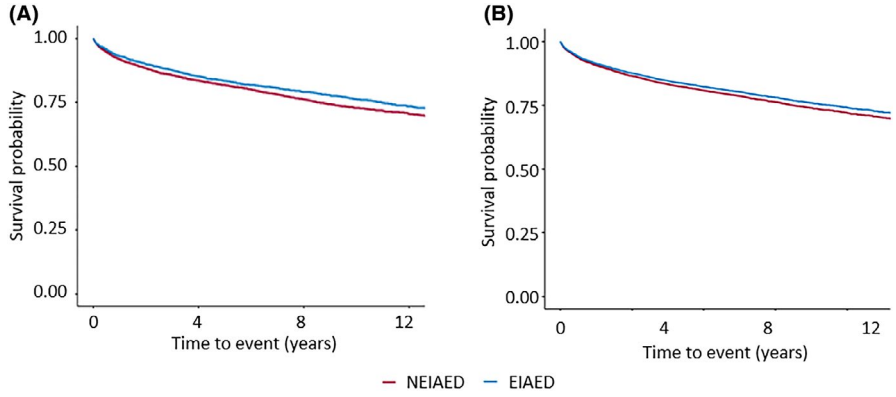

FIGURE 3 Unadjusted and adjusted time-to-event survival curves for enzyme-inducing antiepileptic drug (EIAED) and non-enzyme-inducing antiepileptic drug (NEIAED) treatment groups. (A) Unadjusted survival (time-to-event) models to compare the time to a cardiovascular event for individuals in the two treatment groups. Time-to-event is defined as the time from the index date (date of diagnosis/study start date) to either the first cardiovascular event or the time of censoring, whichever came first. (B) Survival model adjusted for age, sex, smoking status, total antiepileptic drug prescription time (the total length of time for which an individual was prescribed either EIAEDs or NEIAEDs), a coprescription of antiplatelets, anticoagulants, or statins, or a previous diagnosis of hypertension, dyslipidemia, diabetes, thromboembolism, significant arrhythmia, ischemic heart disease, atrial fibrillation, cardiac arrest, myocardial infarction, stroke, or heart failure

EIAEDs compared to NEIAEDs (adjusted hazard ratio = .95, 95% CI = .86–1.05).

4.1 | Major cardiovascular events in case and control cohorts

Previous studies have found an increased risk of stroke and myocardial infarction for people with epilepsy.[24–26] A recent systematic review found hazard ratios of 1.09–2.85 for stroke and 1.09–1.48 for myocardial infarction.[26] It is possible that people with epilepsy may have reduced physical activity, different diets, or increased rates of obesity. Stress, anxiety, and depression are also common with epilepsy and could impact other cardiovascular risk factors.[27] These lifestyle-related cardiovascular risk factors were not measured in this study due to the inconsistency of documentation in routinely collected data. Another reason may be that epilepsy caused by atherosclerotic cerebrovascular disease may precede major cardiovascular events caused by the atherosclerotic cardiovascular disease. This may be independent of AED use, or AEDs may promote risk. Cardiac syncope can occasionally be misdiagnosed as epilepsy, with these cases having an increased risk of significant arrhythmias.[28] AEDs can rarely cause significant arrhythmias, which could increase risk of significant cardiovascular events and death.[29,30]

Less favorable lipid profiles have previously been noted in people with epilepsy.[31,32] Although this has been mostly found in relation to EIAEDs, it is possible that NEIAEDs may also increase metabolic cardiovascular risk. For example, sodium valproate is commonly prescribed and is known to increase body weight and may increase the risk of developing metabolic syndrome.[33,34] Epileptic seizures themselves may have a negative effect on the cardiovascular system via seizure-induced hypoxia, sympathetic activation, or ictal arrhythmias.[35] Seizure frequency and AED doses, which also may be associated with cardiovascular risk, cannot currently be measured accurately in the routinely collected data within the SAIL Databank.

Increasing age, male sex, smoking, deprivation, diabetes, dyslipidemia, and previous cardiovascular events (ischemic heart disease, heart failure, atrial fibrillation, stroke, and thromboembolism) were significantly associated with major cardiovascular events (Table 3). Antiplatelets, anticoagulants, and statins were also significantly associated with major cardiovascular events. We hypothesize that these medications are markers for an increased underlying cardiovascular risk, given that they are normally prescribed to individuals with an increased underlying cardiovascular risk profile or for secondary prevention. Other variables were not significantly associated with altered risk of major cardiovascular events.

4.2 | Major cardiovascular events in the EIAED and NEIAED cohorts

This study did not find a significant difference in survival between the EIAED and NEIAED groups when adjusting for covariates. Previous studies have suggested a link between EIAEDs and increased serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and non-HDL-C compared with the use of NEIAEDs or no AEDs.[8,12] A recent study found a higher rate of diagnosis

TABLE 3 Adjusted hazard ratios for major cardiovascular events in the case (epilepsy) versus control group and EIAED versus NEIAED group

Variable	Group	Hazard ratio	95% CI	*p*
Case (epilepsy) vs. control group				
Group	Control (reference)	1.0		
	Epilepsy	**1.58**	1.51–1.63	<.001
Age	Age 18 years (reference)	1.0		
	Each additional year	1.**06**	1.05–1.06	<.001
Sex	Male (reference)	1.0		
	Female	**.82**	.78–.87	<.001
Smoker	Nonsmoker (reference)	1.0		
	Smoker	**1.09**	1.03–1.15	<.001
Deprivation	WIMD quintile 1 (reference, most deprived)	1.0		
	Each additional quintile	**.94**	.92–.95	<.001
Coprescriptions	Antiplatelet	**2.74**	2.56–2.92	<.001
	Anticoagulants	**1.78**	1.68–1.88	<.001
	Statins	**1.50**	1.41–1.59	<.001
Comorbidities	Diabetes	**1.14**	1.05–1.23	.002
	Dyslipidemia	**.84**	.76–.93	<.001
	Hypertension	1.00	.95–1.07	.801
Previous CV events	Ischemic heart disease	**1.18**	1.05–1.34	.008
	Heart failure	**1.86**	1.60–2.16	<.001
	Atrial fibrillation	**1.24**	1.10–1.40	<.001
	Myocardial infarction	1.10	.96–1.27	.171
	Stroke	**1.91**	1.63–2.23	<.001
	Thromboembolism	**2.09**	1.30–3.37	.002
	Arrhythmia	.75	.47–1.17	.203
	Cardiac arrest	1.33	.79–2.26	.287
EIAED vs. NEIAED group				
Group	NEIAED (reference)	1.0		
	EIAED	.95	.86–1.05	.300
Age	Age 18 years (reference)	1.0		
	Each additional year	**1.04**	1.04–1.04	<.001
Sex	Male (reference)	1.0		
	Female	**.84**	.77–.91	<.001
Smoker	Nonsmoker (reference)	1.0		
	Smoker	**1.18**	1.08–1.30	.001
Deprivation	WIMD quintile 1 (reference, most deprived)	1.0		
	Each additional quintile	.97	.94–1.00	.087
Coprescriptions	Antiplatelet	**2.38**	2.13–2.67	<.001
	Anticoagulants	**1.92**	1.73–2.13	<.001
	Statins	**1.63**	1.47–1.81	<.001
Comorbidities	Diabetes	1.15	1.00–1.33	.054
	Dyslipidemia	**.83**	.70–.99	.040
	Hypertension	**1.13**	1.03–1.25	.014

(Continues)

TABLE 3 (Continued)

Variable	Group	Hazard ratio	95% CI	*p*
Previous CV events	Ischemic heart disease	1.11	.87–1.41	.396
	Heart failure	1.34	.99–1.82	.056
	Atrial fibrillation	1.16	.93–1.44	.187
	Myocardial infarction	1.03	.80–1.34	.805
	Stroke	**2.22**	1.88–2.63	<.001
	Thromboembolism	.70	.10–4.98	.720
	Arrhythmia	1.09	.45–2.63	.846
	Cardiac arrest	1.08	.40–2.94	.870

Hazard ratios in bold are significantly different to 1 ($p < .05$).

Abbreviations: CI, confidence interval; CV, cardiovascular; EIAED, enzyme-inducing antiepileptic drug; NEIAED, non-enzyme-inducing antiepileptic drug; WIMD, Welsh Index of Multiple Deprivation.

of hyperlipidemia in a cohort started on EIAEDs compared with NEIAEDs.[36]

Other studies have addressed the risk of cardiovascular events, according to AED enzymatic properties, for people prescribed AEDs for epilepsy *and* other indications.[35,36] These studies found no significant difference in stroke risk in those prescribed EIAEDs and NEIAEDs.[37,38] One study noted a slight increase in myocardial infarction risk in those prescribed EIAEDs, a risk difference of 1.39/1000.[38] It is possible that the effect of EIAEDs on lipid profiles is dominated by a considerable risk from epilepsy itself, independent of any differential metabolic effect of epilepsy medication type on cardiovascular risk. It would seem therefore that although EIAEDs are associated with metabolic changes related to vascular risk, this does not necessarily lead to an increased risk of major cardiovascular events when compared to NEIAEDs.

The NEIAED group had a slightly higher rate of cardiovascular events in the unadjusted analysis when compared to the EIAED (unadjusted hazard ratio = 1.12, 95% CI = 1.04–1.20, $p = .004$). This could be because they seem to be prescribed to a slightly older population; 18% of prescriptions in the older than 75 years group are for NEIAED compared to 10.5% for EIAED. Clinicians may preferentially select NEIAED for older frail people to minimize adverse effects. This difference does not remain in the adjusted analysis where age is accounted for. Sodium valproate was the most commonly prescribed NEIAED and is associated with weight gain and other metabolic effects that may increase the risk of cardiovascular events.[33,34]

Increasing age, male sex, smoking, hypertension, and previous stroke were significantly associated with major cardiovascular events (Table 3). As in the epilepsy versus control analysis, antiplatelets, anticoagulants, and statins were also significantly associated with major cardiovascular events (see above for our explanation). Other variables were not significantly associated with increased risk of major cardiovascular events.

4.3 | Study strengths

This study includes a large number of individuals (10 241 cases, 35 145 controls), followed up for a long period (study window of 15 years, mean follow-up of 6.90 years, 313 330 person-years), with documentation of a large number (6572) of cardiovascular events. Population-level routinely collected data were used, which reduces recruitment bias and enables detailed capture and adjustment for cardiovascular covariates and events. EIAED or NEIAED prescription duration was accounted for in the analysis. Using population-level data enabled the control cohort to be matched on year of entry into the study, helping to account for changes in health care provision with time.

Previous studies have limited their analysis to stroke and myocardial infarction risk, whereas this study also considers other significant cardiovascular events. This study has also taken into account a wider range of vascular risk factors than other studies that do not consider as many potential confounding factors such as age, sex, and relevant coprescriptions.[5,25]

4.4 | Study limitations

Routinely collected EHR data are not primarily collected for research purposes, can be incomplete, and may contain inaccurate diagnosis codes. The method that was used to identify epilepsy cases within the SAIL Databank has been previously estimated to have a sensitivity of 84% and a specificity of 98%.[18]

Not all cardiovascular risk factors were included in this analysis; for example, physical activity levels, family history, and diet were not included, as they are difficult to obtain accurately from routinely collected data. BMI was excluded from analysis due to high percentage of missing values. Smoking was included in the analysis, but there was a high

level of missing data on smoking status (around one third of the epilepsy cohort), which was assigned nonsmoker status based on estimates of populations who smoke. Epilepsy factors such as severity, syndrome, and seizure frequency that may have an influence on cardiovascular outcomes were not included in this study, as they are not accurately recorded in the routinely collected EHR data used in this study. The group of people prescribed NEIADs were older than the group of people prescribed EIADs, and although we did adjust for age, this might be an important factor. A minimum of 6 months of data coverage prior to and after epilepsy diagnosis was specified as an inclusion criterion, to ensure that epilepsy diagnoses were new. This might not have been long enough to exclude all prevalent cases; however, 95% of the cases had at least 2 years of data prior to their diagnosis, and the mean length of data prior to diagnosis was 3.5 years.

Only people with epilepsy who were taking AEDs were included, as it has been previously found that this gives more accurate epilepsy case ascertainment in routinely collected data.[18] It therefore cannot be said whether it is the epilepsy, the AEDs, or both that increase cardiovascular risk. Also, the AED dosage was not available to include in the analysis. The mean length of follow-up was 6 years in this study. Cardiovascular disease can potentially take longer than this to develop, and so cardiovascular events that occurred after a longer time period will not have been included.

4.5 | Impact

This study demonstrates that adults with epilepsy who are taking AEDs are more likely to experience major cardiovascular events than the general population after accounting for relevant comorbidities and treatments. It is therefore important that health care professionals and people with epilepsy prioritize identification and treatment of cardiovascular disease and its risk factors. For example, making dietary changes, increasing physical activity levels, stopping smoking, and treating hypertension and hypercholesterolemia can all reduce the risk of developing cardiovascular events.

Previous studies have demonstrated that EIAEDs could increase cholesterol and lipid levels. However, this study does not support an increase in major cardiovascular events at a population level. This is important when changes from EIAEDs to NEIAEDs are being considered, as the risks of breakthrough seizures may not be outweighed by the benefits of switching from EIAEDs to NEIAEDs.

5 | Conclusions

Overall, this study suggests that individuals with epilepsy who are taking AEDs are at a significantly greater risk of experiencing major cardiovascular events than the general population. This is corroborated by other studies, highlighting the need for rigorous management of cardiovascular risk in people with epilepsy who have been prescribed AEDs.

Our study has not observed any significant difference in the rates of major cardiovascular events in those prescribed EIAEDs and NEIAEDs, which merits further investigation and may have important implications for treatment selection in clinical practice.

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CONFLICT OF INTEREST

W.O.P. has received consultancy fees from GPW Pharma and Arvelle therapeutics for work unrelated to this study and an investigator grant from UCB Pharma for work unrelated to this study. None of the other authors has any conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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