Stroke and Ischemic Heart Disease With Enzyme-inducing Antiseizure Medications: Time to Change Prescribing Habits

Abstract

Importance: Enzyme-inducing antiseizure medications (eiASMs) have been hypothesized to be associated with long-term risks of cardiovascular disease.

Objective: To quantify and model the putative hazard of cardiovascular disease secondary to eiASM use.

Design, Setting, and Participants: This cohort study covered January 1990 to March 2019 (median [IQR] follow-up, 9 [4–15], years). The study linked primary care and hospital electronic health records at National Health Service hospitals in England. People aged 18 years or older diagnosed as having epilepsy after January 1, 1990, were included. All eligible patients were included with a waiver of consent. No patients were approached who withdrew consent. Analysis began January 2021 and ended August 2021.

Exposures: Receipt of 4 consecutive EI ASMs (carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, or topiramate) following an adult-onset (age >/=18 years) epilepsy diagnosis or repeated exposure in a weighted cumulative exposure model.

Main Outcomes and Measures: Three cohorts were isolated, 1 of which comprised all adults meeting a case definition for epilepsy diagnosed after 1990, 1 comprised incident cases diagnosed after 1998 (hospital linkage date), and 1 was limited to adults diagnosed with epilepsy at 65 years or older. Outcome was incident cardiovascular disease (ischemic heart disease or ischemic or hemorrhagic stroke). Hazard of incident cardiovascular disease was evaluated using adjusted propensity-matched survival analyses and weighted cumulative exposure models.

Results: Of 10,916,166 adults, 50,888 (.6%) were identified as having period-prevalent cases (median [IQR] age, 32 [19–50] years; 16 584 [53%] female), of whom 31,479 (62%) were diagnosed on or after 1990 and were free of cardiovascular disease at baseline. In a propensity-matched Cox proportional hazards model adjusted for age, sex, baseline socioeconomic status, and cardiovascular risk factors, the hazard ratio for incident cardiovascular disease was 1.21 (95% CI, 1.06–1.39) for those receiving eiASMs. The absolute difference in cumulative hazard diverges by more than 1% and greater after 10 years. For those with persistent exposure beyond 4 prescriptions, the median hazard ratio increased from a median (IQR) of 1.54 (1.28–1.79) when taking a relative defined daily dose of an eiASM of 1 to 2.38 (1.52–3.56) with a relative defined daily dose of 2 throughout a maximum of 25 years' follow-up compared with those not receiving an eiASM. The hazard was elevated but attenuated when restricting analyses to incident cases or those diagnosed when older than 65 years.

Conclusions and Relevance: The hazard of incident cardiovascular disease is higher in those receiving eiASMs. The association is dose dependent and the absolute difference in hazard seems to reach clinical significance by approximately 10 years from first exposure.

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Commentary

People with epilepsy have a 2-3-fold increased risk of dying prematurely, and about 15% suffer sudden cardiac death (SCD).[1,2] In a recent study, patients with epilepsy taking antiseizure medications (ASMs) had a 58% higher adjusted risk of having a major cardiovascular event than matched controls.[3] Cardiac complications in epilepsy include (1) Seizure-related events like ictal bradycardia, asystole, ventricular tachycardia, ventricular fibrillation, atrial fibrillation, myocardial infarction, and Takotsubo cardiomyopathy (especially with tonic-clonic convulsions), (2) Epilepsy-related outcomes such as cardiac autonomic dysfunction and the "epileptic heart," and (3)

Treatment-related events like ASM-induced arrhythmias and hyperlipidemia.[1] Some sodium channel blocking (SCB) ASMs can contribute to cardiac arrhythmias, and the U.S. Food and Drug Administration recently asked manufacturers of all SCB ASMs for additional research after announcing warnings about the theoretical risk of lamotrigine.[4]

The possibility that hepatic enzyme-inducing (EI) ASMs raise the risk of cerebrovascular diseases has been studied. Josephson et al. examined whether EI ASMs raise the risk of the incident composite outcome of ischemic heart disease, angina, transient ischemic attack (TIA) and ischemic or hemorrhagic stroke.[5] Their retrospective, open-cohort study analyzed electronic health records of adults with epilepsy in the United Kingdom between 1990 and 2019 in 3 groups.[5] The "period-prevalent cohort" sought to determine the risk of this outcome among 31,479 patients taking EI

ASMs compared to a group taking non-EI ASMs. An "incident cohort" determined the outcome risk associated with EI ASM in patients newly diagnosed with epilepsy. The third group comprised patients in the first cohort aged 65 years and older.

EI ASMs were broken into a group that strongly induces hepatic cytochrome P450 isozymes (carbamazepine, phenobarbital, phenytoin, and primidone) and a group of weak inducers (eslicarbazepine, oxcarbazepine, rufinamide, and topiramate). These were compared to non-EI ASMs. Exposure was defined as any patient who received 4 consecutive prescriptions for an EI ASM following the diagnosis of epilepsy. In the first cohort, the prevalence of hypertension, type II diabetes mellitus, atrial fibrillation, osteoporosis, depression, anxiety, depression, dyslipidemia, and use of a lipid-lowering medication were higher in the non-EI ASM group (p < or = .001), but lipid profiles were not different from the EI ASM group.

Myocardial infarction, angina, TIA, and ischemic and hemorrhage stroke were each significantly higher in the EI ASM than the non-EI ASM group. The hazard ratio (HR) was 1.21 for the composite of these outcomes, but weak EI ASMs had a lower HR than strong ones. Interestingly, the difference between groups was small during the first 8 to 10 years, but substantially diverged in years 10 to 25 of follow-up. The adjusted cumulative HRs were 1.54 and 2.38 for EI ASM daily doses of 1 and 2, respectively, relative to the daily dose defined by the World Health Organization. This dose-response effect supports the conclusion that EI ASMs increase the risk of ischemic heart disease, angina, TIA, and ischemic and hemorrhagic stroke. When the analysis was limited to the cohort of incident cases and to the cohort of older patients, the effect size was attenuated.

The authors[5] argue that the greater risk of ischemic heart disease and stroke is likely due to the EI properties of these ASMs and not the SCB mechanism of action. This is supported by the fact that among the strong EI ASMs, half are SCBs and half are GABA agonists, whereas all the weak EI ASMs are primarily SCBs. That is, if sodium channel blockade was a cause of the outcome, then the risk should be higher in the weak—than in the strong-inducer group, which was not the case.

A limitation of this study is the combination of angina and TIA, which are diagnosed clinically, together with myocardial infarction and ischemic and hemorrhage stroke which are diagnosed using objective laboratory and imaging biomarkers.

Enzyme induction can increase hepatic cholesterol production. Chronic use of EI ASMs like carbamazepine and phenytoin can lead to higher total and low density lipoprotein cholesterol, triglyceride, C-reactive protein, and homocysteine levels.[6,7] One might suppose that this is the mechanism behind the current study's findings, but the authors found that only about 4.3% of the association was due to incident hyperlipidemia and that more patients in the non-EI ASM group were taking lipid-lowering drugs at baseline.[5] Thus, it appears likely that the increased risk of cardiovascular disease with EI ASMs has another cause. Induction of the metabolism of statins is one likely mechanism. Another mechanism by which EI ASMs may raise the risk of cardiovascular events is the hepatic enzyme induction of the metabolism of

antiypertensive and anticoagulant drugs, rendering them less effective. For example, international normalized ratios can fall in patients taking warfarin along with carbamazepine, phenytoin, and barbiturates, and carbamazepine (but not lamotrigine or levetiracetam) renders cholesterol-lowering drugs less effective.[8,9]

In contrast to the current study, another recent study found no difference in cardiovascular events between EI and non-EI ASM groups.[3] Methodological differences included a smaller cohort of 10,241 epilepsy patients, use of a more liberal definition of EI ASM exposure, and not tracking the dose of each ASM prescription. An important difference was that the epilepsy patients were followed for a mean of 6 (maximum 15) years compared to a median of 9 (maximum 29) years in the study by Josephson et al.[5] This may account for the lack of difference between the 2 groups, because the latter study found that the cumulative hazard was only marginally higher over the first 8 to 10 years, but then there was continued annual divergence by more than 1% through year 25 suggesting a chronic, cumulative effect with persistent use of EI ASMs.

Other groups have examined the occurrence of SCD in both patients with epilepsy and with the use of ASMs. In one, SCD was defined as either a witnessed natural death with abrupt loss of consciousness within 1 hour of acute symptoms, or an unwitnessed, unexpected death of a previously healthy person with no evidence of a non-cardiac cause.[2] Among 926 SCD cases and 9832 controls, patients with epilepsy had a SCD HR = 2.8. Moreover, patients with uncontrolled epilepsy had a SCD HR = 5.8. Current use of ASMs had a HR = 2.6 compared to past use of ASM use which had a HR = 1.4. The highest risk of SCD was among patients with poorly controlled epilepsy currently taking ASMs (HR = 6.4). The authors[2] found that the use of SCB ASMs carried a higher risk of SCD, even among non-epilepsy patients (HR = 3.0).[2] In a Finnish study of patients taking ASMs, the odds ratio of autopsy proven SCD was 2.6 when compared to survivors of acute coronary events.[10]

The current study adds additional evidence to the literature indicating that persistent (more than 10 years) use of strong EI ASMs may cause a significantly increased risk of ischemic heart disease and ischemic and hemorrhagic stroke. This study, and the existing literature on cardiovascular events and SCD, combined with the known negative drug–drug interactions and hyperlipidemia resulting from the use of EI ASMs, suggests that if healthcare providers switch patients from EI ASMs to non-EI ASMs then persons with epilepsy may experience improved health and a longer lifespan.

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