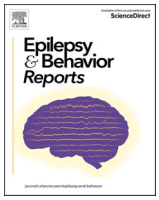
Epilepsy & Behavior Reports 29 (2025) 100738

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr



Management recommendations to reduce cardiac risk in chronic epilepsy

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ARTICLE INFO

Keywords:
Arrhythmia
Echocardiogram
Electrocardiogram
Hyperlipidemia
Hypertension
Ischemic heart disease
Sodium channel blockade
Sudden cardiac death

ABSTRACT

Multifactorial lines of evidence in adults point to a critical linkage between chronic epilepsy and elevated risk for cardiovascular disease and premature cardiac death. Diverse pathophysiological processes appear to be involved that include accelerated atherosclerosis, myocardial infarction, abnormal autonomic tone, heart failure, atrial and ventricular arrhythmias, and hyperlipidemia. Seizure-induced surges in catecholamines and hypoxia may be conducive to cardiovascular damage and the Epileptic Heart condition. The current review provides a systematic strategy for clinical management to reduce risk for cardiovascular disease in adult patients with epilepsy. The proposed approach includes adherence to cardiovascular risk guidelines, incorporation of standard monitoring using electrocardiographic and echocardiographic markers, and regular assessment of plasma lipid profiles. Attention is drawn to the arrhythmogenic risks associated with antiseizure medications (ASMs) with sodium channel blocking properties that can disrupt cardiac conduction and repolarization and predispose to ventricular and atrial arrhythmias. Caution is warranted regarding the use of enzyme-inducing ASMs that can increase plasma lipid levels. The ultimate goals of the proposed management recommendations are to mitigate cardiac risk and reduce premature cardiac death in individuals with chronic epilepsy.

1. Introduction

Chronic epilepsy is a major public health problem, as it afflicts 50 million people worldwide including 3 million adults and 470,000 children in the United States alone [1]. Extensive multifactorial evidence points to a critical linkage between chronic epilepsy and increased risk for cardiovascular disease [1–5]. The supporting data derive from population studies, hospital-based cohort studies, autopsy studies, state-of-the-art electrocardiographic (EKG) and echocardiographic investigations, and reviews of markers of lipid plasma levels associated with coronary and systemic atherosclerotic disease. Several articles in this special issue [5–7] have summarized evidence of a brain–heart connection responsible for elevated risk for cardiac events in patients afflicted with epilepsy, especially when the condition is refractory to medical management.

An important emerging concept is the Epileptic Heart, defined as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and hypoxia leading to electrical and mechanical dysfunction" [2]. A syndromic approach to this clinical entity with standard clinical tests has been specified [3]. These include: EKG, echocardiogram, autonomic function evaluation using heart rate variability (HRV), arrhythmia risk assessment, and determination of plasma lipid levels. A recent population study by Li and colleagues [4] underscores the observation that the deleterious impact of chronic epilepsy applies not only to the heart but also to the structural integrity of the brain, as evidenced by elevated incidence of stroke and transient ischemic attacks in individuals with longstanding epilepsy.

DeGiorgio and colleagues [8,9] provided encouraging results that management of traditional cardiovascular risk factors with smoking cessation, treatment of hypertension, reduction of hyperlipidemia, and

Abbreviations: ARREST, Amsterdam Resuscitation Studies; ASCVD, Atherosclerotic cardiovascular disease; ASM, antiseizure medication; CASH, Cardiac Arrest Study Hamburg; CAST, Cardiac Arrhythmia Suppression Trial; CDC, Centers for Disease Control and Prevention; EKG, electrocardiogram; EMU, epilepsy monitoring unit; FDA, Food and Drug Administration; HDL, high-density lipoprotein; HFpEF, heart failure with preserved left ventricular ejection fraction; HRV, heart rate variability; ILAE, International League Against Epilepsy; LDL, low-density lipoprotein; LQTS, long QT syndrome; MORTEMUS, Mortality in Epilepsy Monitoring Unit Study; rMSSD, root mean square of successive differences of R-R intervals; SUDEP, sudden unexpected death in epilepsy; TWA, T-wave alternans.

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https://doi.org/10.1016/j.ebr.2024.100738
Received 11 November 2024; Received in revised form 20 December 2024; Accepted 20 December 2024
Available online 25 December 2024

diabetes management following the Atherosclerotic Cardiovascular Disease (ASCVD) guidelines from the American Heart Association and the American College of Cardiology [10] reduced deaths from ischemic heart disease in patients with epilepsy from 10.79% to 6.19% (42.6% reduction) of all epilepsy deaths from 1999 to 2017 [8,9]. This decline was contemporaneous with a 16.4% reduction in cardiac mortality in the general population [11,12]. Importantly, the ASCVD risk scores remained higher in people with than without epilepsy, including higher rates of hypertension, diabetes, heart disease, and stroke [13].

Our main objective is to propose recommendations for clinical management to reduce long-term cardiovascular risk in patients with epilepsy. Currently, while guidelines have been adopted in the United Kingdom to improve diagnosis of asystole vs syncope as the cause of transient loss of consciousness (https://www.nice.org.uk/guidance/CG137) and internationally to prevent sudden unexpected death in epilepsy (SUDEP) [14], no guideline for reducing cardiovascular risk in patients with epilepsy has been approved [15], underscoring the need for progress on this topic.

2. Initial evaluation

Our recommendations, which are specified in Table 1, are for adult patient management following the initial visit for evaluation of first seizure or initial episode of transient alteration or loss of consciousness. At the initial visit, 12-lead EKGs should be recorded in all patients and evaluated for signs of cardiac pathology, such as long QT syndrome (LQTS). Evidence of QT-interval prolongation (> 450 ms in men or >470 ms in women) merits genetic testing to identify underlying genetic causes, some of which may result in channelopathies causing cardiac conduction or repolarization abnormalities with a concurrent susceptibility to epilepsy. A 13–42% rate of misdiagnosis of asystole and bradyarrhythmias as epilepsy has been reported [16]. Thus, the possibility of cardiac asystole should be addressed with an ambulatory EKG recording or an implantable loop EKG recorder [16]. In all patients with an initial clinical diagnosis of seizure or epilepsy, a baseline 12-lead EKG should be obtained, as many antiseizure medications (ASMs) may cause changes in cardiac conduction.

3. Management recommendations for patients with chronic epilepsy

Cardiovascular comorbidities have been reported in 62% to 82% of patients with chronic epilepsy and are major factors in their sudden premature death [2–5,17–19]. Compounding the effects of seizure-induced surges in catecholamines and hypoxia, underlying causes of cardiac dysfunction include altered lipid profiles and side effects of enzyme-inducing ASMs, leading to accelerated atherosclerosis, and the proarrhythmic influences of certain ASMs, particularly sodium channel blocking drugs. A review in this issue reports the multifold increases in cardiac mortality and comorbidities in population-based studies of patients with epilepsy [5]. The Amsterdam Resuscitation Studies (ARREST) found that risk of cardiac arrest due to ventricular fibrillation was 2.8-fold higher in people with chronic epilepsy than in those without epilepsy [20]. In the Oregon Sudden Unexpected Death Study [21], the sudden cardiac death rate was 4.4% per year among people with epilepsy, which corresponds to a rate that is 4.5-fold greater than SUDEP (Fig. 1). These studies demonstrate that individuals with epilepsy suffered sudden cardiac arrest at an earlier age, specifically ~55 years of age compared to those without epilepsy at ~63 years. Notably, in two thirds (66%) of the patients with chronic epilepsy, no seizures immediately preceding the sudden cardiac arrest were observed by witnesses familiar with their companions' seizures [21].

Studies emphasize age as a crucial factor in adopting a patient management regimen based on pathophysiologic considerations (Table 1, Fig. 1). Furthermore, in patients with poorly controlled seizures, the progressive impact of seizure-induced cardiac damage culminates in structural alterations and electrical instability with enhanced risk for life-threatening arrhythmias [22,23], a risk that may persist even if seizure control is achieved in cases of irreversible structural damage to the heart [2].

Table 1
Management recommendations for patients with chronic epilepsy.

Adult patients aged <45 years.
- Follow ASCVD guidelines [10] for reducing cardiovascular risk
  - o Recommend smoking cessation, treat hypertension, reduce hyperlipidemia, manage diabetes and metabolic syndrome
  - o Consider switching from enzyme-inducing to non-enzyme-inducing ASMs esp. in patients with elevated plasma lipid levels
- Record baseline routine resting 12-lead EKG[a]
  - o Evaluate EKG for rhythm abnormalities, Q waves indicating prior MI, repolarization abnormalities, e.g., QT-interval prolongation
  - o Repeat EKG when using ASMs associated with conduction abnormalities
- Follow ILAE guidelines for SUDEP prevention [68]

Patients aged ≥45 years or patients with clinical symptoms of cardiac disease:[b]
- Follow ASCVD guidelines [10] for reducing cardiovascular risk
  - o Recommend smoking cessation, treat hypertension, reduce hyperlipidemia, manage diabetes and metabolic syndrome
  - o Consider switching from enzyme-inducing to non-enzyme-inducing ASMs esp. in patients with elevated plasma lipid levels
  - o Consider alternatives to valproate in patients with metabolic syndrome
- Record baseline routine resting 12-lead EKG[a]
  - o Evaluate EKG for rhythm abnormalities, Q waves indicating prior MI, repolarization abnormalities, e.g., QT-interval prolongation
  - o Repeat EKG when using ASMs associated with conduction abnormalities
- Avoid ASMs with sodium-channel blockade, switch to ASMs without this action
- If 12-lead EKGs are abnormal, then consider AECG recording with Holter or EKG patch:
  - o Analyze recordings for clinically significant arrhythmias
  - o Analyze EKG recordings for T-wave alternans, rMSSD HRV
- If significant EKG abnormalities are detected, refer for cardiology consult to evaluate for arrhythmias and functional abnormalities: LV stiffness, LV diastolic filling pressure, and left atrial volume

Key: AECG = ambulatory electrocardiogram; ASCVD = Atherosclerotic cardiovascular disease; ASM = Antiseizure medication; EKG = Electrocardiogram; HRV = heart rate variability; ILAE = International League Against Epilepsy; LV = Left ventricular; MI = Myocardial infarction; rMSSD = root mean square of successive differences of R-R intervals; SUDEP = sudden unexpected death in epilepsy

[a] Resting 12-lead EKG is recommended for all patients admitted to the Epilepsy Monitoring Unit or Emergency Department.

[b] E.g., symptoms including exercise intolerance, chest pain, irregular pulse, palpitations.

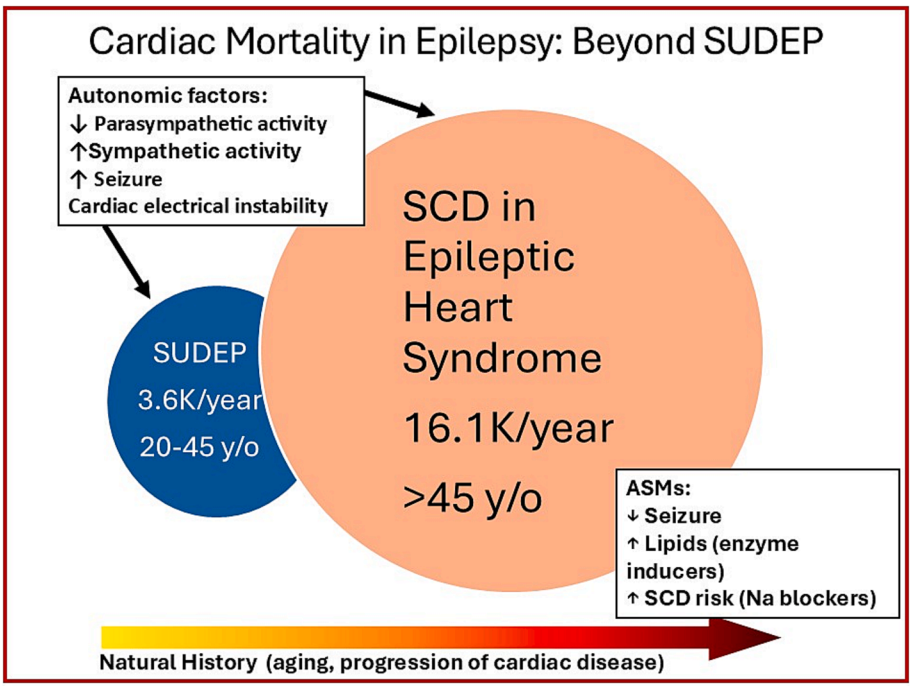

Fig. 1. Legend: Venn diagram of the interrelationship between sudden cardiac death (SCD) and sudden unexpected death in patients with epilepsy (SUDEP). SUDEP incidence data of 3600 cases/year are from Thurman et al [68] and Harden et al [14]. SCD incidence data are from Stecker et al. [21], Zack and Kobau [72], and Benjamin et al [73]. ASMs = antiseizure medications. Republished with permission from Elsevier from Verrier et al [2].

Based on this collective evidence, the following fundamental approaches are recommended:

- **Optimize seizure control**: This recommendation is emphasized because recurrent seizures, especially those with features suggestive of increased sympathetic tone, constitute a critical factor in increasing risk for the Epileptic Heart condition.
- **Reduce cardiovascular risk factors**: In particular, we recommend following ASCVD guidelines from the American Heart Association and American College of Cardiology [10].
- **Tailor antiseizure medication(s)**: Based on patient-specific factors and risks, careful ASM selection needs to be undertaken to avoid exacerbation of existing cardiovascular risks.
- **Perform comprehensive cardiac evaluation**: In patients with multiple cardiovascular risk factors or evidence of the Epileptic Heart condition, comprehensive cardiac evaluation, including 12-lead EKG at baseline and at regular intervals, ambulatory EKG, echocardiogram, and a referral to cardiology for comprehensive evaluation may be indicated.

Long-term management of patients with epilepsy, particularly those with refractory epilepsy, should involve a comprehensive approach that incorporates cardiovascular health as an essential aspect of overall patient care. Patients should be risk stratified initially based on traditional cardiovascular risk factors, which include age, hypertension, diabetes, family history, smoking status, lipid profile and sedentary behavior [10]. In addition to assessment of seizure frequency and ASM tolerance at regular intervals, a broader screen should be undertaken to include cardiac symptoms, such as chest pain, irregular pulse, palpitations, and poor exercise tolerance. Even in patients whose seizures are controlled, cardiovascular abnormalities may persist or new risks may develop in patients with longstanding epilepsy and therefore require continued monitoring.

3.1. Management recommendations for patients aged ≥45 years or patients with known cardiac risks

Age and disease duration are important factors in determining management strategy as disease progression in both epilepsy and cardiac risk may develop as a function of time (Fig. 1). Patients aged 45 years or older are at particular risk for heart disease and atrial and ventricular arrhythmias [4,17,18]. Patients should be educated about healthy lifestyle habits, including smoking cessation, balanced diet, and adequate activity, as recommended by the United States Centers for Disease Control and Prevention (CDC), and ASCVD score guidelines for reducing cardiovascular risk should be followed [10].

3.1.1. Lipid profile and metabolic syndrome

The classic enzyme-inducing ASMs, for example, carbamazepine and phenytoin, are known to induce hepatic enzymes in the cytochrome p450 system that may predispose to elevated plasma lipid levels and reduce efficacy of lipid-lowering agents [24], which can in turn accelerate atherosclerosis [25,26]. Consequently, there may be greater risk for cardiovascular events including transient ischemic attacks, stroke, and myocardial infarction. Valproate has been found to decrease high-density lipoprotein (HDL) levels and to augment low-density lipoprotein (LDL) and triglyceride levels [27]. Additionally, carbamazepine and valproate have been implicated in the metabolic syndrome, with adverse effects on cardiovascular health [28]. Based on these findings, our main recommendations in individuals with elevated lipids or taking lipid-lowering agents is to consider initiating or switching to ASM therapy without enzyme inducing properties or adverse effects on the lipid profile. For patients with obesity and diabetes, an alternative to valproate should be considered to avoid worsening their cardiovascular risk and accelerating atherosclerotic disease.

3.1.2. Cardiac conduction and ASMs with sodium channel blocking properties

Extensive evidence indicates that cardiac sodium channel blockade, especially in patients with cardiovascular disease, can lead to

conduction abnormalities and serious cardiac arrhythmias including wide-complex ventricular tachycardia. The Cardiac Arrhythmia Suppression Trial (CAST), which enrolled post-myocardial infarction patients with ventricular tachyarrhythmias, reported that sodium channel blockade with flecainide and encainide was arrhythmogenic and resulted in an excess incidence of death compared to placebo [29]. In the Cardiac Arrest Study Hamburg (CASH) trial in patients with prior cardiac arrest, the sodium channel blocking agent propafenone resulted in an increase in all-cause mortality [30].

In 2021, the United States Food and Drug Administration (FDA) issued a safety warning on the cardiac effects of lamotrigine and recommended avoidance of this agent in patients with various conduction disorders such as heart block, ventricular arrhythmias, or cardiac disease. The FDA stated that concomitant use of lamotrigine with other sodium channel blocking agents may increase the risk of arrhythmia [31]. Whereas increased morbidity and mortality have not been verified with lamotrigine [32], based on this FDA alert, we recommend caution in prescribing sodium channel blocking ASMs, including carbamazepine, phenytoin [33] and lacosamide [34–36] in patients with EKG evidence of conduction abnormalities. In these patients, sodium channel blocking ASMs should be avoided or replaced in favor of non-sodium channel blocking agents. In the event that alternative ASMs cannot be utilized, we recommend careful baseline evaluation and regular cardiac monitoring using 12-lead EKGs and multiday ambulatory EKG monitors, and referral to cardiology in those with known pre-existing cardiac disease.

3.1.3. Electrocardiogram

A standard 12-lead EKG is a cost-effective and readily accessible screening test across medical facilities in both rural and urban settings and should be incorporated into the routine care of patients with chronic epilepsy on a regular basis. Specific focus should be on detection of myocardial injury and risk for serious atrial and ventricular arrhythmias.

3.1.3.1. PR interval. This interval reflects conduction through the atrioventricular node and its prolongation implies slowing of conduction between the atria and ventricles. Lacosamide is a sodium channel blocking ASM whose main mechanism of action is to slow inactivation of voltage-gated sodium channels, which can lead to PR-interval prolongation in a dose-dependent fashion. Clinically, various cardiac arrhythmias have been reported with lacosamide use, including bradycardia, atrioventricular nodal block, ventricular tachycardia, and, rarely, complete heart block [34–36]. A baseline 12-lead EKG should be obtained prior to initiation of therapy to assess pre-existing conduction defects, and a follow-up EKG during therapy should be obtained for reassessment. For patients with baseline bradycardia, heart block, and other arrhythmias, alternative ASMs should be considered.

3.1.3.2. ST-segment and Q waves. The standard indicator of myocardial ischemia, ST-segment depression, has been found to be present in ~40% of epileptic seizures [37]. Risk for myocardial infarction in patients with chronic epilepsy is in the range of 1.5- to 4.8-fold greater than in the overall population [38,39] and ST-segment elevation may occur. The occurrence of pathological Q waves in the 12-lead EKG may reveal previously undetected "silent" myocardial infarction.

3.1.3.3. QT interval. This parameter has been widely utilized in evaluation of arrhythmia risk from cardiac disease. Cardiac repolarization abnormalities have been found during interictal periods in approximately one third of patients with drug-resistant epilepsy [40–47].

A recent study [47] retrospectively analyzed QT intervals in 12-lead EKGs recorded in >18,000 patients in the Mayo Clinic (Rochester MN) Epilepsy Registry spanning 15 years. Kaplan-Meier analysis reported a significant hazard ratio of 1.9 for all-cause mortality based on a QT interval cutoff of ≥448 ms (Fig. 2). The study demonstrated the potential utility of QT-interval monitoring in individuals with chronic epilepsy. Certain mainstream ASMs can prolong the QT interval, such as phenobarbital, phenytoin, and carbamazepine [19].

3.1.3.4. T-wave alternans. Risk for life-threatening ventricular arrhythmias and sudden cardiac death due to repolarization abnormalities can also be measured noninvasively by T-wave alternans (TWA), defined as a beat-to-beat alternation in the ST-segment and/or T-wave morphology. TWA's utility has been validated in patient cohorts with diverse cardiac diseases [48] and is abnormally elevated during the interictal period in individuals with chronic epilepsy [23,49–51]. The increased TWA levels observed in epilepsy are comparable to those found in post-myocardial infarction patients who are susceptible to malignant ventricular arrhythmias (Fig. 3) [23,50,51]. We found that TWA is abnormally elevated in patients with chronic epilepsy but not in those who are newly diagnosed [23]. TWA can be tracked using ambulatory EKG monitors [48] and patches [23] and during exercise tolerance testing using the FDA-cleared modified moving average analysis technique [48].

3.1.3.5. Routine use of 12-lead EKG in the epilepsy monitoring unit. At our institution, we monitor all patients admitted to the epilepsy monitoring unit (EMU) with a resting 12-lead EKG. The rationale is that if patients have sufficiently severe and recurring seizures, the potential for cardiac damage is elevated due to cardiotoxic effects of catecholamines and recurrent hypoxia. In general, we recommend that significant EKG

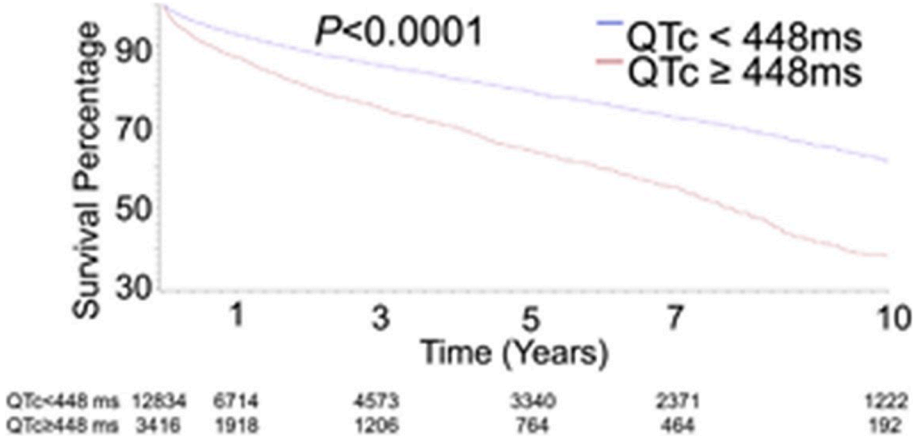

Fig. 2. Legend: Kaplan-Meier survival plots of mortality as predicted by prolonged QT interval for patients with index evaluation for seizure or epilepsy (Cohort 1; "sensitive"), comparing patients based on the optimized ≥448 ms cutpoint. Reprinted with permission from Elsevier from Chahal et al [47].

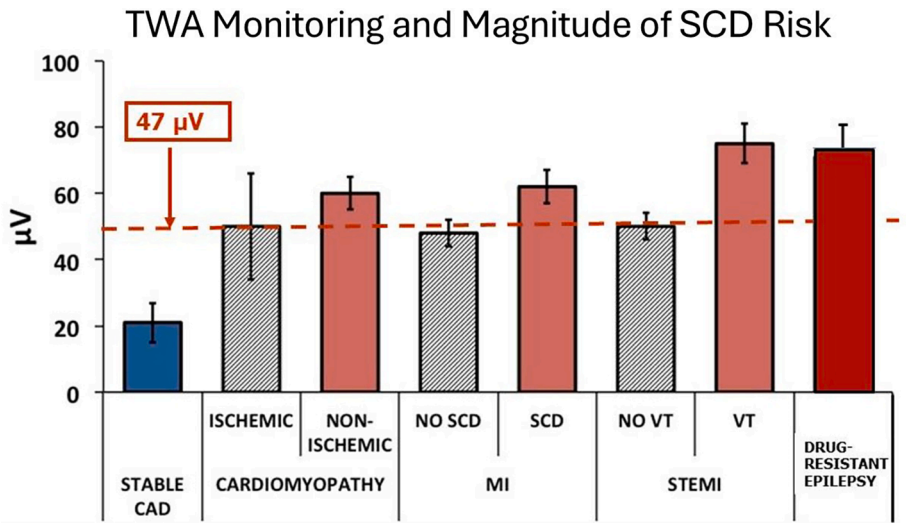

Fig. 3. Legend: T-wave alternans (TWA) and magnitude of sudden cardiac death (SCD) risk in ambulatory electrocardiographic monitoring. Patients with chronic epilepsy exhibit maximum 24-hour TWA in the severely abnormal range (>60 μV), similarly to patients who experience ventricular tachycardia (VT) following ST-segment elevation myocardial infarction (STEMI). CAD, coronary artery disease; MI, myocardial infarction; SCD, sudden cardiac death. Republished with permission from Elsevier from Verrier et al. [2].

changes suggestive of myocardial injury or enhanced risk for atrial or ventricular arrhythmias merit a cardiology consult.

Although the EKG is a valuable tool in management of epilepsy patients, in the Mayo Clinic (Rochester MN) Epilepsy Registry, only 44% of patients with a probable epilepsy diagnosis had a resting 12-lead EKG recording at the initial hospital visit [47]. This limited use of the standard EKG is a likely result of the lack of practice guidelines in the United States. Furthermore, this experience varies from the United Kingdom, where the guidelines (https://www.nice.org.uk/guidance/CG137) recommend routine use of the EKG in epilepsy diagnosis. EKGs are also underutilized in the EMU, as a survey showed that only 65% of Canadian EMUs employed continuous EKG monitoring [52].

3.1.3.6. Multiday ambulatory EKG monitoring. We recommend multiday ambulatory EKG monitoring using wireless EKG patches, which can permit disclosure of infrequent rhythm abnormalities such as atrial fibrillation and ventricular tachyarrhythmias in patients whose 12-lead EKGs are abnormal and in patients reporting paroxysmal symptoms such as palpitations. An implantable cardiac monitor study of patients with drug-resistant epilepsy [53] reported a high incidence of clinically significant arrhythmias, including 9.7% of patients with serious cardiac arrhythmias necessitating cardiac intervention. A nationwide analysis of over one million hospitalizations of epilepsy patients in the United States [54] estimated that nearly 10% experienced atrial fibrillation. The presence of atrial fibrillation in chronic epilepsy patients deserves further attention in light of its attendant increased risk for stroke and myocardial infarction.

Ambulatory Holters and EKG patches not only increase the EKG monitoring period for cardiac events but also enable analysis of autonomic tone using heart rate variability (HRV). Among the most widely employed measures of parasympathetic tone is "root mean square of successive differences of R-R intervals" (rMSSD). This time-domain HRV parameter correlates inversely with risk for sudden cardiac death [55–57]. A meta-analysis determined that chronic epilepsy patients exhibit lower rMSSD values than are present in the general population [58].

3.1.4. Echocardiographic assessment of left ventricular stiffness and left atrial enlargement

State-of-the-art echocardiography revealed that chronic epilepsy can predispose to stress-related cardiomyopathy characteristic of heart failure with preserved left ventricular ejection fraction (HFpEF) [6,59–64] attributable to repeated episodes of sympathetic nerve hyperactivity. Zhao and coworkers [65] proposed based on animal studies that release of catecholamines at the neurocardiac junction during seizures results in cardiac myofilament damage, extracellular matrix deposition, fibrosis, and inflammation. Furthermore, recurrent epileptic seizures can set the stage for HFpEF with potential for left ventricular hypertrophy [60,66]. In particular, Doege et al [67] observed a 1.56-fold increase in heart failure diagnoses in individuals with compared to those without chronic epilepsy. Collectively, these investigations underscore the potential application of echocardiography to identify changes in structural cardiac substrate that compromise cardiac mechanical function and increase risk for serious atrial and ventricular arrhythmia.

3.2. Management recommendations for adult patients aged < 45 years

In adults with epilepsy aged 20 to 45 years, premature demise has been largely attributed to the entity of SUDEP, which claims one case/thousand adults/year or ~2750 to 3600 deaths annually in the United States alone [14,68]. The International League Against Epilepsy (ILAE)'s definition for SUDEP is: "A sudden, unexpected death in persons with epilepsy with or without evidence of a seizure preceding the death, in which there is no evidence of other disease, injury, or drowning that caused the death" [14] specifically omitting cardiac causes by definition [69]. The Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) determined that postictal respiratory arrest leading to cardiac asystole was causally linked to the terminal event in SUDEP [1,70]. In addition to minimizing the risk for SUDEP [14], seizure reduction, especially those with features of increased sympathetic tone, should be a management goal as uncontrolled seizures in this population may also lead to the Epileptic Heart condition. Similar management recommendations for the older individuals also apply to this age group.

Reducing cardiac risk in younger patients, such as those with Dravet syndrome [71] or genetic conduction defects, is beyond the scope of this review.

4. Future Directions and Challenges

The current recommendations as summarized in Table 1 are based on substantial evidence of the pathophysiologic bases for cardiovascular mortality as a function of age in patients with chronic epilepsy.

Cardiovascular risk stratification and management early in the epilepsy disease course, with vigilant symptomatic screening and utilization of standard clinical laboratory tests, EKGs, echocardiography, and full cardiac assessments, have the potential for improving overall medical management. Future studies evaluating the presence of coronary calcium in patients with epilepsy could prove helpful in determining the effects of epilepsy in accelerating heart disease. A vast resource of digitized EKG data and echocardiograms as well as plasma lipid profiles is available, for example in the CDC Wonder database [8,9], the Mayo Clinic Epilepsy Registry [47], the U.K. Biobank [18], the Canadian Longitudinal Study on Aging [4], and others [5] to test the applicability of our proposed management recommendations. It is not premature to plan sizeable randomized clinical trials to evaluate the merit of a syndromic approach to the Epileptic Heart condition to improve detection of cardiac risk and to develop improved strategies for reduction of premature cardiac death in individuals afflicted with recurring epileptic seizures.

Ethical Statement

This manuscript complies with all aspects of Elsevier's principles of ethics. As it is a review article, it does not provide original data from preclinical or clinical studies.

CRediT authorship contribution statement

Trudy D. Pang: Writing – review & editing, Writing – original draft, Conceptualization. **Richard L. Verrier:** Writing – review & editing. **Steven C. Schachter:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Trudy D. Pang, M.D., reports a relationship with Stratus, Inc. (Irving TX) that includes: Medical Advisory Board membership and speaking and lecture fees. She also reports a relationship with UCB that includes speaking and lecture fees. She also reports that she is the guest editor of the special issue to which this manuscript is submitted.

Richard L. Verrier, Ph.D., reports a relationship with Stratus, Inc. (Irving TX) that includes: Medical Advisory Board membership and speaking and lecture fees. He also reports a relationship with UCB that includes speaking and lecture fees.

Steven C. Schacter, M.D., declares no competing financial interests or personal relationships that could appear to influence the work reported in this paper.

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