The Interplay of Epilepsy, Anti-Seizure Medications, and Cardiac Health: A Comprehensive Review

I. Executive Summary

This report synthesizes findings from five recent studies—Ha et al. (2025), Wang et al. (2023), Lee-Lane et al. (2021), Cross et al. (2024), and Li et al. (2024)—to elucidate the intricate relationship between epilepsy, anti-seizure medications (ASMs), and cardiovascular health, with a particular focus on cardiac arrhythmias and major cardiovascular events. A consistent observation across the literature is the elevated risk of cardiovascular complications in individuals with epilepsy, often conceptualized as the "epileptic heart." This heightened risk is attributed to both the inherent nature of the neurological disorder itself and, in a more complex and sometimes contradictory manner, to the use of ASMs.

While epilepsy is unequivocally linked to an increased long-term risk of arrhythmias and overall cardiovascular morbidity, the specific impact of individual ASMs presents a nuanced picture. Certain ASMs, particularly those that block sodium channels, have been implicated in cardiac conduction delays and proarrhythmic effects. However, other large-scale studies suggest that some ASMs may be associated with a reduced incidence of arrhythmias or no discernible increase in major cardiovascular events. These divergent findings underscore the critical need for comprehensive cardiac monitoring and tailored risk management strategies in epilepsy patients, emphasizing the ongoing research required to clarify the precise mechanisms and long-term effects of ASMs on cardiac function.

II. Introduction

Background on Epilepsy and Cardiovascular Comorbidity

Epilepsy stands as a globally prevalent neurological disorder, affecting approximately 50 million individuals worldwide.[1] Individuals diagnosed with epilepsy consistently exhibit higher mortality rates compared to the general population.[2] A robust and increasingly discernible relationship exists between neurological and cardiac function, with research revealing numerous connections between the two systems.[5] People living with epilepsy face an elevated risk for various cardiovascular conditions, including heart disease, hypertension, atrial fibrillation, and hyperlipidemia.[1] Conversely, individuals with pre-existing cardiovascular disease and associated risk factors demonstrate an increased susceptibility to developing epilepsy, a risk that extends beyond stroke-related etiologies.[5] This bidirectional influence highlights a complex interplay rather than a simple co-occurrence of conditions.

The Concept of the "Epileptic Heart"

The profound connection between epilepsy and cardiac health has led to the emergence of the "epileptic heart" concept, first proposed by Richard Verrier, Trudy Pang, and their colleagues in 2020.[1] This concept describes a heart and coronary vasculature that sustain damage over time due to chronic epilepsy. The proposed mechanisms for this damage include repeated episodes of hypoxemia, the toxic effects of surges in catecholamines (such as adrenaline) released during seizures, and accelerated atherosclerosis.[1] Such chronic insults can lead to significant electrical and mechanical dysfunction within the heart, thereby increasing the risk of various cardiovascular problems, including sudden cardiac death (SCD).[3] While SCD in the general population is most commonly caused by ventricular fibrillation, people with epilepsy face a nearly threefold increased risk for SCD compared to the general population.[1] This distinct pathophysiology underscores the importance of considering cardiac health as an integral part of epilepsy management.

Role of Anti-Seizure Medications (ASMs)

Anti-seizure medications (ASMs) serve as the cornerstone of epilepsy treatment.[2] While indispensable for controlling seizures, these medications have also been associated with adverse cardiac outcomes. The mechanisms underlying these effects are diverse, ranging from influences on lipid metabolism, which can increase the risk of ischemic heart disease, to specific actions on cardiac ion channels, potentially elevating the risk of cardiac arrhythmias.[9] The dual nature of ASMs—as both therapeutic agents and potential contributors to cardiovascular risk—necessitates a thorough understanding of their cardiac safety profiles. The ongoing research aims to clarify these specific risks and the underlying mechanisms, providing a more comprehensive picture for clinical decision-making.

III. Review of Individual Studies

This section provides a detailed summary of five pivotal papers that investigate the complex relationship between epilepsy, ASMs, and cardiac health.

A. Ha et al. (2025): "Association between Anti-Seizure Medications and Cardiac Arrhythmias in Patients Undergoing Ambulatory Electroencephalographic and Electrocardiographic Monitoring"

- **Core Thesis:** This study aimed to evaluate the association between demographic variables, anti-seizure medications (ASMs), and the incidence of cardiac arrhythmias in patients undergoing ambulatory video-electroencephalographic (EEG)-electrocardiographic (ECG) monitoring (AVEEM).[12]
- **Main Arguments:** ASMs are widely prescribed for epilepsy, yet some have been linked to adverse cardiac outcomes, including arrhythmias.[12] There was a recognized need to investigate cardiac arrhythmias in epilepsy patients within ambulatory settings, utilizing concurrent EEG and ECG monitoring to capture real-world data.[13]
- **Key Findings:** Out of 3695 patients monitored, approximately 28% (1029 patients) experienced a cardiac arrhythmia, with non-sustained supraventricular tachycardia (SVT) being the most frequent type (19%, 695 patients).[12] Contrary to

some general concerns, multivariable analysis revealed that carbamazepine (OR 0.72, 95%CI 0.53-0.98, p = 0.03), lamotrigine (OR 0.57, 95%CI 0.44-0.73, p<0.001), and lacosamide (OR 0.63, 95%CI 0.43-0.92, p = 0.02) were associated with
fewer cardiac arrhythmias.[12] This observed association was not dependent on the dose of the medication.[12] Importantly, the study found no commonly-prescribed ASMs associated with an
increased risk of cardiac arrhythmias, nor was there a significant association between ASM use and dynamic QTc interval changes.[12]

- **Methodology:** This was a retrospective observational study conducted in Australia between 2020 and 2023, involving patients aged 16 years and older who underwent AVEEM. Logistic regression was employed to analyze the association between variables. ASMs were not withdrawn during the monitoring period, reflecting real-world clinical practice.[12]
- **Significance:** The findings of Ha et al. challenge the prevailing assumption that all ASMs uniformly increase arrhythmia risk, suggesting that some may possess antiarrhythmic properties. This study highlights the need for further large clinical prospective studies to confirm these observations and to elucidate the mechanisms behind any potential antiarrhythmic effects of ASMs.[12]
- **Strengths:** The study benefited from a large patient cohort (3695 individuals) and the use of concurrent EEG-ECG monitoring, which allowed for detailed detection of arrhythmias in a real-world setting.[12]
- **Limitations:** As an observational study, it cannot establish direct causality between ASM use and arrhythmia outcomes. The specific types of ASMs beyond the three highlighted were not detailed for all patients, and the median monitoring duration of 6.8 days, while clinically relevant, might not be long enough to capture all intermittent or rare arrhythmias.[12]
- **Reception:** Published in February 2025, the long-term reception and influence of this study are yet to be fully established. No citation count was available in the provided information.[12]

B. Wang et al. (2023): "Epilepsy and Long-Term Risk of Arrhythmias"

- **Core Thesis:** The primary objective of this study was to assess the long-term association of epilepsy with cardiac arrhythmias, specifically considering the potential roles of genetic predisposition and anti-seizure medications (ASMs) in any observed associations.[4]

- **Main Arguments:** Previous research predominantly focused on transient changes in cardiac function during or immediately after seizures in people with epilepsy, leaving the long-term risk of cardiac arrhythmias poorly characterized.[4] The authors argued that people with epilepsy consistently exhibit a higher prevalence of cardiac comorbidities, which are recognized as crucial contributors to premature death.[4] Thus, investigating the long-term impact and the influence of ASMs and genetic factors was essential.[4]
- **Key Findings:** The study, which included 329,432 individuals (2699 with epilepsy), revealed that people with epilepsy experienced a significantly increased risk of *all cardiac arrhythmias* (hazard ratio 1.36, 95% CI 1.21–1.53), atrial fibrillation (HR 1.26, 95% CI 1.08–1.46), and other cardiac arrhythmias (HR 1.56, 95% CI 1.34–1.81) when compared to individuals without epilepsy.[4] A notable finding was that these associations were
  not modified by genetic predisposition as indicated by polygenic risk scores (PRS).[4] Furthermore, individuals with epilepsy who were using ASMs, particularly carbamazepine and valproic acid, were found to be at a
  higher risk for cardiac arrhythmias. This observation was corroborated by drug target Mendelian randomization (MR) results.[4]
- **Methodology:** This was a large-scale population-based study that analyzed data from the UK Biobank, encompassing individuals recruited between 2006 and 2010. Cox proportional hazards models and competing risk models were utilized to examine the association between epilepsy history and the long-term incidence risk of cardiac arrhythmias and their subtypes. The study also incorporated polygenic risk scores (PRS) to investigate genetic susceptibility and evaluated the role of ASMs by integrating observational and drug target Mendelian randomization (MR) evidence.[4]
- **Significance:** This study provides robust evidence for the persistent long-term risk of cardiac arrhythmias in people with epilepsy, demonstrating that this risk is independent of genetic predisposition. The findings underscore the critical need for regular heart rhythm monitoring and proactive management in epilepsy patients, especially for those being treated with carbamazepine and valproic acid, to mitigate the risk of further cardiovascular complications.[4]
- **Strengths:** The study's strengths lie in its large population-based cohort, which enhances generalizability, and its long follow-up period. The use of robust statistical methods, including genetic analyses (PRS and MR), allowed for a more rigorous assessment of causality and the control of confounding factors.[4]
- **Limitations:** The study's reliance on observational data for ASM use means that, despite sophisticated analytical techniques, some residual confounding might still be present.[4] Specific details regarding individual ASM dosages or precise

durations of use were not explicitly detailed in the available information.
- **Reception:** The paper was published in September 2023. No explicit citation count or detailed reception information was available in the provided material.[1]

C. Lee-Lane et al. (2021): "Epilepsy, Antiepileptic Drugs, and the Risk of Major Cardiovascular Events"

- **Core Thesis:** The central aim of this study was to ascertain whether epilepsy and the use of antiepileptic drugs (AEDs), encompassing both enzyme-inducing (EIAEDs) and non-enzyme-inducing (NEIAEDs) types, are associated with an increased risk of major cardiovascular events. Furthermore, the study sought to determine if there was a notable difference in this risk between patients treated with EIAEDs and those treated with NEIAEDs.[2]
- **Main Arguments:** Individuals with epilepsy exhibit higher mortality rates than the general population, with cardiovascular events being a significant contributing factor.[2] Prior research had suggested a link between AEDs and an elevated risk of cardiovascular events, such as stroke, myocardial infarction (MI), and arrhythmias.[2] Concerns were particularly raised about older EIAEDs, which might be associated with more adverse effects and could alter metabolic pathways related to vascular risk, including elevated cholesterol levels.[2] Despite these links, there was a perceived lack of direct evidence regarding the effect of AEDs on *major cardiovascular events*.[2]
- **Key Findings:** The study found that individuals with epilepsy who were prescribed AEDs had a significantly increased risk of *major cardiovascular events* (adjusted hazard ratio = 1.58, 95% confidence interval [CI] = 1.51–1.63, p <.001) when compared to matched population controls.[2] A crucial finding was the absence of a notable difference in the incidence of major cardiovascular events between those treated with EIAEDs and those treated with NEIAEDs (adjusted HR = 0.95, 95% CI = 0.86–1.05, p =.300).[2] Commonly prescribed EIAEDs included phenytoin, phenobarbital, carbamazepine, and primidone, while NEIAEDs encompassed sodium valproate, lamotrigine, levetiracetam, gabapentin, and pregabalin.[2]
- **Methodology:** This study employed a retrospective matched cohort design, utilizing anonymized, routinely collected healthcare data from Wales, UK, spanning from 2003 to 2017. A large cohort of 10,241 epilepsy cases was identified and matched to 35,145 controls based on age, gender, deprivation quintile, and year of study entry. Cox proportional hazard models were used for

statistical analysis, with extensive adjustments for numerous baseline demographic and clinical covariates, including smoking status, diabetes, hypertension, dyslipidemia, and previous cardiovascular events.[2]

- **Significance:** This research underscores the critical importance of cardiovascular risk management as an integral component of clinical care for individuals with epilepsy. The finding that EIAEDs were not associated with a greater risk of major cardiovascular events compared to NEIAEDs is particularly significant, suggesting that the risks of breakthrough seizures from switching from EIAEDs may not be outweighed by perceived cardiovascular benefits in terms of major events.[2]
- **Strengths:** The study's strengths include its large cohort size, providing robust statistical power, and a long follow-up period (mean 6.90 years, 313,330 person-years), which allowed for the observation of cardiovascular events over time.[2] The use of population-level routinely collected data minimized recruitment bias and enabled detailed capture and adjustment for cardiovascular covariates. The study also adopted a comprehensive definition of major cardiovascular events, broader than some previous research.[2]
- **Limitations:** Inherent limitations of using routinely collected electronic health record (EHR) data include potential incompleteness and inaccuracies in diagnosis codes. The study was unable to include all relevant cardiovascular risk factors (e.g., physical activity, family history, diet) due to data unavailability, and a significant portion of smoking status data was missing. Furthermore, epilepsy-specific factors such as severity, syndrome, and seizure frequency could not be accurately accounted for. As the study only included people with epilepsy taking AEDs, it could not definitively differentiate the risk contribution from epilepsy itself versus the AEDs.[2] AED dosage information was also not available.[2]
- **Reception:** The article has been cited 57 times.[2] Its finding regarding the lack of significant difference in major cardiovascular events between EIAEDs and NEIAEDs has been a point of discussion, as it contrasts with some other studies that suggest EIAEDs might increase cardiovascular risk markers or specific events like hyperlipidemia.[2]

D. Cross et al. (2024): "Sudden Cardiac Death or Ventricular Arrhythmia in Patients Taking Levetiracetam or Oxcarbazepine"

- **Core Thesis:** This study aimed to assess whether levetiracetam, an antiseizure medication, is associated with an increased risk of ventricular arrhythmia and sudden cardiac arrest (VA/SCA) when compared with oxcarbazepine.[17]

- **Main Arguments:** Concerns had been raised regarding levetiracetam's potential to prolong the QT interval and consequently increase the risk of sudden cardiac death, which could have significant implications for patient safety and prescribing practices.[17] The study sought to clarify this cardiac risk by comparing levetiracetam to oxcarbazepine, an active comparator medication not known to prolong the QT interval.[17]
- **Key Findings:** The study found that levetiracetam *did not demonstrate an increased risk* of VA/SCA when compared to oxcarbazepine (hazard ratio 0.79, 95% CI 0.42-1.47).[17] These findings do not support the concerns for cardiac risk that would warrant restriction of levetiracetam use or the requirement for routine cardiac monitoring.[17]
- **Methodology:** This was a retrospective cohort study that utilized administrative claims data from the OptumLabs Data Warehouse, covering the period from January 2010 to December 2019. The study identified 104,655 new levetiracetam users and 39,596 new oxcarbazepine users. A new user design was employed, and propensity score weighting was used to balance the cohorts and minimize bias. Weighted Cox regressions were then performed to evaluate the association of levetiracetam with the combined endpoint of sudden cardiac death or ventricular arrhythmia.[17]
- **Significance:** This study provides Class II evidence suggesting that levetiracetam is not associated with an increased risk of VA/SCA compared to oxcarbazepine. These results are important for potentially alleviating clinical concerns and informing prescribing practices, particularly given levetiracetam's widespread use in epilepsy management.[17]
- **Strengths:** The study's strengths include its very large sample size, the use of a new user design, and the application of propensity score weighting with an active comparator, all of which contribute to reducing potential confounding and enhancing the validity of the findings.[17]
- **Limitations:** As a retrospective study relying on administrative claims data, it may lack granular clinical details that could influence outcomes. The generalizability of the findings is primarily to the Medicare-insured older population represented in the OptumLabs Data Warehouse.[17]
- **Reception:** The paper was published in May 2024. As of April 2024, it had been cited by at least two other articles.[17] No direct citation count was available in the provided information.[17]

E. Li et al. (2024): "Risk Assessment of Arrhythmias Related to Three Antiseizure

Medications: A Systematic Review and Single-Arm Meta-Analysis"

- **Core Thesis:** This systematic review and single-arm meta-analysis aimed to preliminarily evaluate the incidence of cardiac arrhythmia associated with the use of three common newer-generation anti-seizure medications—lacosamide (LCM), levetiracetam (LEV), and perampanel (PER)—and to provide guidance for the treatment and management of epilepsy.[10]
- **Main Arguments:** ASMs are the first-line treatment for seizure disorders, but they can induce adverse reactions, including cardiac arrhythmias.[10] Both epilepsy itself and ASMs are linked to an elevated risk of cardiovascular diseases, with ASMs potentially prolonging the QT interval by affecting ion channels, thereby influencing cardiac rhythm.[10] There was a recognized need to investigate the arrhythmogenic effects of these newer ASMs.[10]
- **Key Findings:** The meta-analysis reported a pooled incidence of arrhythmias of 0.005 (0.5%, 95% CI: 0.001-0.013) for the LEV group and 0.014 (1.4%, 95% CI: 0.003-0.030) for the LCM group.[10] The use of LCM was found to significantly elevate the risk of arrhythmias.[10] Conversely, LEV demonstrated non-significant arrhythmogenic effects.[10] Due to an insufficient number of eligible studies, a meta-analysis for PER could not be conducted, indicating a need for more clinical trials on its arrhythmogenic effects.[10] Further analysis suggested that LCM exhibited proarrhythmic effects, particularly in the context of an already prolonged QT interval.[22] Interestingly, lamotrigine, another sodium channel blocker, showed antiarrhythmic effects with additive QT prolongation in an isolated rabbit heart model.[22] The study also noted that dosage might influence LCM's risk, with a higher pooled incidence observed in fixed-dosage groups compared to stepwise dose increase groups.[10] According to CIOMS criteria, LCM was rated as "frequent" (1.4% incidence) for arrhythmia as an adverse reaction, while LEV was rated as "infrequent" (0.5% incidence).[10]
- **Methodology:** The study employed a systematic review and single-arm meta-analysis approach. Four major databases (PubMed, EMBASE, Cochrane Library, and Web of Science) were searched up to August 2023. Two independent investigators screened articles based on predefined inclusion criteria, focusing on randomized controlled trials (RCTs) or clinical trials involving epilepsy patients treated with LEV, PER, or LCM as monotherapy, with arrhythmia outcomes. Data extraction and quality assessment (using the Cochrane risk of bias tool, RoB 2) were performed by independent reviewers. Pooled incidence rates and 95% confidence intervals were estimated, and heterogeneity was assessed. Publication bias was detected and corrected for the LCM group.[10]

- **Significance:** This study provides valuable evidence for clinicians regarding the relative risk of cardiac arrhythmias associated with commonly used newer ASMs like LCM and LEV. It contributes to the understanding of drug-induced arrhythmias and offers guidance for epilepsy treatment and management, emphasizing the importance of regular electrocardiogram monitoring in patients using ASMs.[10]
- **Strengths:** The study's strengths include its robust systematic review and meta-analysis methodology, comprehensive database search, the use of independent reviewers for screening and data extraction, quality assessment of included studies, and the identification and correction for publication bias in the LCM group.[10]
- **Limitations:** Not all included studies were RCTs, and some were clinical trials where blinding could not be fully implemented, potentially introducing bias. The study acknowledges that epilepsy itself can lead to cardiac arrhythmias, which might introduce confounding that could not be fully accounted for. A subgroup analysis by age was not possible due to data limitations. There was insufficient data for PER to conduct a meta-analysis, and the overall sample size for the meta-analysis was relatively small, potentially leading to an underestimation of arrhythmia incidence. The paper also noted that for novel drugs, long-term adverse effects might still be undiscovered.[10]
- **Reception:** The article was published on February 14, 2024. No explicit citation count was available in the provided information, but the assessment and correction of publication bias suggest a rigorous review process.[10]

IV. Synthesized Analysis: Cross-Study Observations

A. The "Epileptic Heart" Concept and Overall Cardiovascular Risk

A consistent and overarching theme across the reviewed literature is the strong affirmation of a profound, bidirectional relationship between epilepsy and cardiovascular disease. This connection extends beyond traditional cardiovascular risk factors, pointing towards a direct influence of the neurological condition on cardiac health. The concept of the "epileptic heart" serves as a crucial unifying

framework for this understanding.

Evidence indicates that individuals with epilepsy face an increased susceptibility to various cardiovascular conditions, including heart disease, hypertension, atrial fibrillation, and hyperlipidemia.[1] Conversely, individuals with pre-existing cardiovascular disease and associated risk factors exhibit an elevated likelihood of developing epilepsy, even when excluding stroke-related causes.[5] This reciprocal relationship highlights a complex interconnectedness between the brain and heart. The risk of malignant arrhythmias and sudden cardiac death (SCD) is notably higher in epilepsy patients, approaching nearly three times that observed in the general population.[1]

The "epileptic heart" concept, initially proposed by Verrier and colleagues, describes a heart and its coronary vasculature that undergo damage as a direct consequence of chronic epilepsy.[1] This damage is attributed to repeated episodes of hypoxemia, the deleterious effects of excessive catecholamine release during seizures, and accelerated atherosclerosis.[1] These chronic insults culminate in electrical and mechanical dysfunction, thereby increasing the overall risk of cardiovascular problems, including SCD.[3]

Wang et al. (2023) provided compelling population-level evidence reinforcing this understanding. Their study demonstrated that the elevated risk of cardiac arrhythmias persists long-term in individuals with epilepsy, and notably, this association was not modified by genetic predisposition.[4] This observation strengthens the argument that epilepsy itself, rather than merely underlying genetic vulnerabilities, directly contributes to cardiac risk. The implication is that effective management of epilepsy may directly contribute to mitigating cardiac risk, extending beyond general improvements in health.

The consistent references to the "brain-heart axis" across the studies [4] are not merely descriptive. This emphasis highlights the anatomical and functional connections through which neurological events, such as seizures and associated autonomic dysfunction, directly influence cardiac function. The "epileptic heart" is a manifestation of this intricate axis. If seizures precipitate catecholamine surges and hypoxemia leading to cardiac damage, then optimizing seizure control becomes a primary intervention for safeguarding cardiac health, not just for neurological well-being.[13] This perspective suggests the potential for an integrated "cardio-neurology" approach, focusing on interventions that modulate this axis to prevent cardiac complications in epilepsy patients.

Key Takeaways: Epilepsy is a significant and independent risk factor for long-term cardiac arrhythmias and major cardiovascular events. This risk is driven by direct pathophysiological effects on the heart, encapsulated by the "epileptic heart" phenomenon, and is not solely explained by genetic predisposition or traditional cardiovascular risk factors.

B. Impact of Anti-Seizure Medications on Cardiac Health: A Nuanced Landscape

The impact of ASMs on cardiac health is characterized by considerable complexity and, at times, conflicting evidence. This necessitates a drug-specific and context-dependent interpretation rather than a broad generalization. While certain ASMs are indeed linked to proarrhythmic effects or conduction delays, other large-scale studies indicate that some may be neutral or even beneficial in specific arrhythmia contexts.

Generally, ASMs are recognized for their potential to cause adverse cardiac effects, either through their influence on lipid metabolism, which can increase the risk of ischemic heart disease, or through their direct actions on cardiac ion channels, which may elevate arrhythmia risk.[9] Sodium channel blocking ASMs, in particular, have garnered attention due to their potential to affect cardiac sodium channels and increase the risk of sudden cardiac death.[7]

However, a closer examination of individual ASMs reveals a more intricate picture:

- **Lacosamide (LCM):** Ha et al. (2025) reported that LCM was associated with *fewer* cardiac arrhythmias (OR 0.63).[12] This finding stands in direct contrast to the meta-analysis by Li et al. (2024), which concluded that LCM significantly *elevated* arrhythmia risk (pooled incidence 1.4%) and demonstrated proarrhythmic effects, especially in the presence of prolonged QT intervals.[10] This discrepancy is notable, particularly as the latter finding contributed to an FDA warning regarding LCM.[22]
- **Carbamazepine:** Similar to lacosamide, Ha et al. (2025) found carbamazepine associated with *fewer* cardiac arrhythmias (OR 0.72).[12] Yet, Wang et al. (2023) identified carbamazepine (along with valproic acid) as being associated with a *higher risk* for cardiac arrhythmias.[4] Adding to this complexity, Lee-Lane et al. (2021) found
  no notable difference in major cardiovascular events between enzyme-inducing

AEDs (EIAEDs), which include carbamazepine, and non-enzyme-inducing AEDs (NEIAEDs).[2]

- **Lamotrigine:** Ha et al. (2025) observed that lamotrigine was associated with *fewer* cardiac arrhythmias (OR 0.57).[12] Furthermore, in an isolated rabbit heart model, Li et al. (2024) found that lamotrigine demonstrated *antiarrhythmic effects* even with additive QT prolongation.[22] Consistent with these observations, Cross et al. (2024) reported that lamotrigine was *not* associated with an increased risk of ventricular arrhythmia/sudden cardiac arrest (VA/SCA) compared to levetiracetam in older adults, and even showed a *reduced* risk in subgroups with baseline arrhythmia or antiarrhythmic drug use.[19]
- **Levetiracetam (LEV):** Both Li et al. (2024) and Cross et al. (2024) presented findings that suggest a favorable cardiac safety profile for levetiracetam. Li et al.'s meta-analysis indicated that LEV had non-significant arrhythmogenic effects (pooled incidence 0.5%).[10] Cross et al. similarly found LEV was *not* associated with an increased risk of VA/SCA compared to oxcarbazepine.[17]
- **Sodium Channel Blockers (NABs/SCBs) in General:** While the class of sodium channel blockers is broadly a concern, with Wang et al. (2023) noting that people with active epilepsy taking NABs were more likely to have prolonged QRS (OR 2.85) and any cardiac conduction delay (CCD) (OR 1.94) [7], and Lee-Lane et al. (2021) mentioning concerns that SCB ASMs might contribute to cardiac arrhythmias and SCD [9], the specific findings for lamotrigine and lacosamide by Ha et al. (2025) and lamotrigine by Li et al. (2024) and Cross et al. (2024) demonstrate a more nuanced reality.

The direct contradictions observed for lacosamide (Ha et al. suggesting fewer arrhythmias vs. Li et al. indicating elevated risk) and carbamazepine (Ha et al. suggesting fewer arrhythmias vs. Wang et al. indicating higher risk) highlight that a generalized statement about "ASMs and cardiac risk" is insufficient. The effects are highly drug-specific. These disparities could arise from differences in study design (e.g., observational vs. meta-analysis), patient populations, or monitoring duration and methodology. It is plausible that the effects are complex and context-dependent, perhaps antiarrhythmic in some patients or arrhythmia types, but proarrhythmic in others, or at different dosages or durations. This necessitates a more granular approach to cardiac risk assessment, moving beyond broad drug classes to individual agents and specific patient profiles.

A crucial distinction also emerges when comparing acute arrhythmogenic effects with long-term cardiovascular morbidity. Lee-Lane et al. (2021) found no significant difference in *major cardiovascular events* (a broad composite endpoint including MI,

stroke, heart failure) between EIAEDs and NEIAEDs, despite EIAEDs being linked to lipid abnormalities.[2] In contrast, Wang et al. (2023) specifically identified certain ASMs (carbamazepine, valproic acid) as increasing

arrhythmia risk.[4] This suggests that a drug might influence short-term electrical stability (arrhythmia risk) without necessarily increasing the long-term risk of broader cardiovascular events, or vice-versa. The underlying mechanisms, such as direct ion channel effects versus metabolic effects leading to atherosclerosis, are distinct. This implies that clinical monitoring strategies should be tailored to the specific type of cardiac risk being evaluated.

A notable observation is the apparent paradox of sodium channel blockers. While these are generally identified as a class of concern for cardiac conduction delays and arrhythmias [7], studies on lamotrigine (a sodium channel blocker) by Ha et al. (2025) and Li et al. (2024) suggest it may have antiarrhythmic or non-significant effects.[12] This apparent contradiction suggests that the precise mechanism of sodium channel modulation (e.g., enhancing inactivation versus inhibiting activation, as described for lacosamide versus lamotrigine in Li et al. [22]) is critically important. Not all sodium channel blockade translates equally to cardiac safety. This calls for more detailed pharmacological studies to elucidate these nuanced mechanisms.

Key Takeaways: The cardiac effects of ASMs are highly variable and often contradictory across studies, demanding careful interpretation. Distinguishing between acute arrhythmogenic effects and long-term major cardiovascular events is crucial. Sodium channel blockers, while a class of concern, exhibit complex and sometimes unexpected effects on cardiac rhythm depending on the specific drug and its precise mechanism of action.

Table 1: Summary of Key Findings on ASM-Associated Cardiac Risks

ASM	Study (Author, Year)	Primary Cardiac Outcome Assessed	Key Finding	Effect Size (95% CI)	Notes
Carbamazepine	Ha et al. (2025)	Cardiac Arrhythmias	Associated with *fewer* cardiac arrhythmias	OR 0.72 (0.53-0.98)	Not dose-dependent

	Wang et al. (2023)	Long-term Cardiac Arrhythmias	Associated with *higher risk* for cardiac arrhythmias	Not specified	Supported by drug target MR
	Lee-Lane et al. (2021)	Major Cardiovascular Events	No notable difference vs. NEIAEDs	HR 0.95 (0.86-1.05)	As an EIAED
Lamotrigine	Ha et al. (2025)	Cardiac Arrhythmias	Associated with *fewer* cardiac arrhythmias	OR 0.57 (0.44-0.73)	Not dose-dependent
	Li et al. (2024)	Arrhythmia susceptibility (in vitro)	Showed *antiarrhythmic effects*	Decrease in VT incidence	In isolated rabbit heart with QT prolongation
	Cross et al. (2024)	VA/SCA	*Not* associated with increased risk vs. LEV	HR 0.84 (0.67-1.06)	In older adults; reduced risk in subgroups with baseline arrhythmia
Lacosamide	Ha et al. (2025)	Cardiac Arrhythmias	Associated with *fewer* cardiac arrhythmias	OR 0.63 (0.43-0.92)	Not dose-dependent
	Li et al. (2024)	Arrhythmias (meta-analysis)	Significantly *elevated* risk of arrhythmias	Pooled incidence 0.014 (0.003-0.030)	Proarrhythmic, especially with prolonged QT; FDA warning
Levetiracetam	Li et al. (2024)	Arrhythmias (meta-analysis)	Non-significant arrhythmogenic effects	Pooled incidence 0.005 (0.001-0.013)	
	Cross et al. (2024)	VA/SCA	*Not* associated	HR 0.79 (0.42-1.47)	In older adults

			with increased risk vs. oxcarbazepine		
Valproic Acid	Wang et al. (2023)	Long-term Cardiac Arrhythmias	Associated with *higher risk* for cardiac arrhythmias	Not specified	Supported by drug target MR
Phenytoin	Wang et al. (2023)	Cardiac Conduction Delays (CCDs)	Prevalence of any CCD 45.5%	[95% CI 31.7%–58.5%]	As a Sodium Channel Blocker (NAB)
Sodium Channel Blockers (NABs)	Wang et al. (2023)	Prolonged QRS, Any CCD, Prolonged QTc	More likely to have prolonged QRS (OR 2.85), any CCD (OR 1.94), prolonged QTc (OR 1.52)	ORs with 95% CIs	NAB use associated with CCD, active epilepsy not

C. Methodological Approaches and Evidence Strength

The diverse methodologies employed across these studies—ranging from observational cohorts to systematic reviews with meta-analyses and even animal models—provide varying levels of evidence strength and contribute to the observed discrepancies in findings. A comprehensive understanding of the complex interplay between epilepsy, ASMs, and cardiac health is best achieved by integrating findings from these different approaches.

Observational cohort studies, such as those by Ha et al. (2025) using AVEEM data [12], Wang et al. (2023) leveraging the UK Biobank [4], Lee-Lane et al. (2021) utilizing national health records [2], and Cross et al. (2024) employing administrative claims data [17], offer valuable real-world epidemiological evidence. These studies are instrumental in identifying associations and trends within large populations over extended periods.

For instance, Wang et al.'s large sample size and long follow-up provided robust data on long-term arrhythmia risk.[4] Cross et al.'s use of a new user design with an active comparator and propensity score weighting aimed to enhance the comparability of their treatment groups.[17] However, a common challenge for these studies is their susceptibility to confounding factors, as they cannot directly control for all variables in the way a randomized controlled trial can.

Systematic reviews and meta-analyses, exemplified by Li et al. (2024) [10], synthesize evidence from multiple individual trials. This approach increases statistical power and generalizability of pooled incidence rates, and allows for the assessment of heterogeneity and publication bias across the literature. This synthesis is crucial for drawing broader conclusions from fragmented evidence.

Furthermore, animal models, such as the isolated rabbit heart (Langendorff) model mentioned in Li et al. (2024) [22], provide invaluable mechanistic insights. These models allow researchers to characterize the precise effects of drugs on ion channels and cardiac electrophysiology at a cellular or organ level, which can help explain clinical observations or even contradictions seen in human studies. For example, the differing effects of lacosamide and lamotrigine on sodium channels were explored in such a model.[22]

The complementary nature of these diverse methodologies is evident. Observational studies provide the broad strokes of population-level trends and associations, while meta-analyses consolidate existing clinical trial data. Mechanistic studies in animal models offer a deeper understanding of the biological underpinnings. Each method compensates for the inherent limitations of the others. For example, Wang et al.'s integration of Mendelian Randomization [4] represents an attempt to address confounding inherent in observational studies, moving closer to inferring causal relationships.

Despite these advancements, the reliance on large administrative datasets in many studies presents a persistent challenge related to confounding. While powerful for revealing population-level trends, these datasets often lack granular clinical detail, such as the severity of epilepsy, seizure frequency, precise drug dosages, or lifestyle factors like physical activity and diet.[2] Even with robust statistical adjustments like propensity score weighting or extensive covariate adjustment, this missing information can lead to residual confounding. For instance, if patients prescribed certain ASMs tend to have more severe epilepsy, their higher cardiac risk might be attributable more to the underlying disease than to the medication itself, as noted in the limitations of Li et al.'s work.[10] This implies that while associations can be identified, establishing

definitive causality remains challenging without randomized controlled trials specifically designed to evaluate cardiac outcomes.

Key Takeaways: The evidence base regarding epilepsy, ASMs, and cardiac health is strengthened by the application of diverse methodologies, each contributing unique perspectives. However, the inherent limitations of observational data, particularly concerning confounding and the absence of granular clinical detail, pose significant challenges to definitively attributing causality for ASM-related cardiac effects.

Table 2: Overview of Study Designs and Populations

Study (Author, Year)	Study Design	Population/Cohort Size	Key Population Characteristics	Primary Outcomes	Follow-up/Monitoring Duration
Ha et al. (2025)	Retrospective Observational	3695 patients	Median age 40, 64% female, undergoing AVEEM	Cardiac Arrhythmias	Median 6.8 days
Wang et al. (2023)	Population-based Cohort	329,432 individuals (2699 with epilepsy)	UK Biobank data	Long-term Cardiac Arrhythmias, Arrhythmia Subtypes	Recruited 2006-2010 (long-term follow-up)
Lee-Lane et al. (2021)	Retrospective Matched Cohort	10,241 epilepsy cases, 35,145 controls	Adults (≥18), Wales, UK healthcare data	Major Cardiovascular Events	Study window 2003-2017 (mean 6.9 years follow-up)
Cross et al. (2024)	Retrospective Cohort	104,655 LEV users, 39,596 OXC users	Medicare-insured individuals aged 65+	Ventricular Arrhythmia / Sudden Cardiac Arrest (VA/SCA)	2010-2019 (new users)
Li et al. (2024)	Systematic Review &	11 clinical trials, 1031	Patients with epilepsy on	Incidence of Cardiac	Up to August 2023 (search

	Single-Arm Meta-Analysis	participants	monotherapy (LEV, LCM, PER)	Arrhythmia	date)

D. Key Agreements and Discrepancies

While a strong consensus exists on the overall increased cardiovascular risk in individuals with epilepsy, significant discrepancies emerge when examining the specific cardiac effects of individual ASMs, particularly sodium channel blockers. These differences in findings are likely attributable to variations in study design, patient populations, outcome definitions, and analytical methodologies.

Areas of Agreement:

- **Epilepsy Increases Cardiac Risk:** All reviewed papers implicitly or explicitly concur that epilepsy itself is associated with an increased risk of cardiac issues, including arrhythmias and sudden cardiac death.[1] The concept of the "epileptic heart," which posits that chronic epilepsy directly damages cardiac function, is widely acknowledged as a crucial framework for understanding this relationship.[1]
- **Need for Cardiac Monitoring:** Multiple studies consistently advocate for routine cardiological assessment and heart rhythm monitoring as an important component of care for epilepsy patients.[1]
- **Levetiracetam's Favorable Profile:** Both Cross et al. (2024) and Li et al. (2024) suggest that levetiracetam has a non-significant or no increased risk of arrhythmias or sudden cardiac death.[10]
- **Lamotrigine's Favorable Profile:** Ha et al. (2025) and Li et al. (2024) (in an animal model) indicate that lamotrigine may be associated with fewer arrhythmias or even possess antiarrhythmic properties.[12] Cross et al. (2024) also found no increased risk for lamotrigine in older adults.[19]

Areas of Discrepancy:

- **Lacosamide (LCM):** Ha et al. (2025) reported that LCM was associated with *fewer* cardiac arrhythmias.[12] This directly contradicts the findings of Li et al. (2024), whose meta-analysis concluded that LCM significantly *elevated* arrhythmia risk and showed proarrhythmic effects in both human data synthesis and animal models.[10]
- **Carbamazepine:** Ha et al. (2025) found carbamazepine associated with *fewer* cardiac arrhythmias.[12] However, Wang et al. (2023) identified it as being

associated with a
higher risk for cardiac arrhythmias.[4] Adding another layer of complexity, Lee-Lane et al. (2021) found no difference in
major cardiovascular events for enzyme-inducing AEDs (including carbamazepine) versus non-enzyme-inducing AEDs.[2]

- **Sodium Channel Blockers (NABs/SCBs):** While Wang et al. (2023) and Lee-Lane et al. (2021) generally suggest that NABs/SCBs are associated with cardiac conduction delays or an increased risk of sudden cardiac death [7], this broad concern is challenged by the specific findings for lamotrigine and lacosamide by Ha et al. (2025) and for lamotrigine by Li et al. (2024) and Cross et al. (2024).

The discrepancies, particularly for lacosamide and carbamazepine, can be understood by considering the influence of outcome definition and study population. Ha et al. (2025) focused on *any cardiac arrhythmia* detected during short-term ambulatory monitoring [12], whereas Wang et al. (2023) investigated the

long-term incidence risk of cardiac arrhythmias.[4] Li et al. (2024) pooled data from clinical trials for

arrhythmia incidence [10], and Lee-Lane et al. (2021) examined

major cardiovascular events, a broader composite endpoint.[2] These are distinct clinical endpoints, and a medication might indeed exert different effects on each. Furthermore, patient populations vary significantly across studies; for example, Ha et al.'s cohort had a median age of 40 [12], while Cross et al.'s study focused on Medicare-insured individuals aged 65 and older.[20] The underlying cardiac health, presence of comorbidities, and polypharmacy in different age groups or clinical settings could substantially alter the observed drug effects or detected risks. This highlights that clinicians must consider the specific cardiac outcome of concern and the patient's demographic and comorbidity profile when interpreting these studies.

The contradictory findings for the same medications (e.g., lacosamide, carbamazepine) are not simply random variations; they point to an incomplete understanding of the underlying mechanisms. A crucial question arises: why would lacosamide appear protective in one study but proarrhythmic in another? Such inconsistencies could be related to dosage (Li et al. noted dosage influence for LCM [10]), duration of exposure, specific patient susceptibilities (e.g., genetic channelopathies mentioned in [5]), or interactions with other medications. This necessitates that future research moves beyond observational associations to

detailed mechanistic studies and potentially stratified clinical trials to reconcile these contradictions.

Key Takeaways: While the overall cardiac risk associated with epilepsy is well-established, the specific impact of ASMs remains a subject of considerable debate. Discrepancies in findings emphasize the importance of meticulously considering study design, outcome definitions, and patient populations. Resolving these contradictions requires a deeper mechanistic understanding and targeted research efforts.

V. Clinical Implications and Recommendations

The consistent evidence demonstrating an increased cardiovascular risk in individuals with epilepsy mandates a proactive and integrated approach to cardiac risk assessment and management as an essential component of comprehensive epilepsy care. Given the nuanced and sometimes conflicting effects of individual ASMs on cardiac health, personalized treatment decisions and ongoing monitoring are paramount.

People with epilepsy face a significantly higher risk of heart disease, various arrhythmias, and sudden cardiac death.[1] The concept of the "epileptic heart" underscores that chronic epilepsy itself can lead to structural and functional damage to the heart.[1] This pervasive link between epilepsy and cardiac health means that neurologists and cardiologists must collaborate more closely. It is no longer sufficient for neurologists to focus solely on seizure control while cardiologists manage heart conditions in isolation. The "epileptic heart" phenomenon necessitates a holistic, interdisciplinary approach, potentially leading to the development of shared patient management protocols and specialized clinics focusing on neuro-cardiac comorbidities.

Routine cardiological assessment, including electrocardiogram (ECG), is consistently highlighted as an important diagnostic and monitoring tool.[1] The influence of ASM use on cardiac risk is undeniable, yet it is complex. Some ASMs are associated with increased risk (e.g., lacosamide in Li et al. [10], carbamazepine and valproic acid in Wang et al. [4]), while others appear to have no increased risk or even beneficial effects (e.g., levetiracetam in Cross et al. [17] and Li et al. [10], and lamotrigine in Ha et al. [12] and Li et al. [22]). The critical need for careful heart rhythm monitoring and management to mitigate

the risk of sudden cardiac death and long-term cardiac dysfunction is consistently emphasized.[4]

The contradictory findings regarding ASM-specific cardiac effects, particularly for medications like lacosamide and carbamazepine, indicate that a "one-size-fits-all" approach to ASM selection is inappropriate for patients with or at risk of cardiac issues. Clinicians should consider a patient's individual cardiac risk factors, pre-existing cardiac conditions, and the specific ASM's known cardiac profile (even if conflicting across studies). For instance, if a patient has a history of arrhythmias, an ASM like lacosamide might be used with extreme caution, given the findings by Li et al. [10], despite the seemingly contradictory results from Ha et al..[12] Conversely, levetiracetam or lamotrigine might be preferred due to their more favorable cardiac safety profiles.[10] This necessitates a shift towards precision medicine in epilepsy management.

The emphasis on "routine cardiological assessment" [1] and "regular heart rhythm monitoring" [4] suggests that cardiac monitoring should be proactive rather than merely reactive to symptoms. Given the inherent risk of sudden cardiac death in epilepsy [1] and the potential for certain ASMs to induce arrhythmias [10], baseline and periodic ECGs should be considered standard practice. The identified "unmet need to investigate cardiac arrhythmias in patients with epilepsy in ambulatory settings" [13] further implies that more extensive monitoring (e.g., Holter monitoring, wearable devices) could be beneficial for early detection, particularly in high-risk patient populations.

Recommendations:

- **Implement Routine Cardiac Screening:** Establish and implement routine baseline and periodic cardiac screening protocols, including ECG, for all epilepsy patients. This is especially crucial for individuals with long-standing epilepsy or additional cardiovascular risk factors.
- **Personalize ASM Selection:** When initiating or adjusting ASM therapy, carefully consider the specific cardiac safety profile of each medication, particularly for patients with pre-existing cardiac conditions. Prioritize ASMs with demonstrated neutral or beneficial cardiac effects where appropriate.
- **Patient and Caregiver Education:** Educate patients and their caregivers about the increased cardiovascular risk associated with epilepsy and the critical importance of adherence to both epilepsy and cardiovascular management plans.
- **Promote Lifestyle Modifications:** Actively encourage and support lifestyle modifications aimed at reducing traditional cardiovascular risk factors, such as

smoking cessation and effective management of hypertension, diabetes, and hyperlipidemia.[6]

VI. Future Research Directions

Despite significant advancements, the existing literature reveals critical knowledge gaps and areas requiring further investigation to refine understanding and improve patient care. A primary focus for future research should be the resolution of conflicting data regarding ASM cardiac effects and the acquisition of deeper mechanistic insights.

Several studies highlight unmet needs and calls for future research:

- Further large clinical prospective studies are essential to confirm findings on ASM-associated arrhythmias and to clarify any potential antiarrhythmic properties.[12]
- More clinical trials are specifically needed to assess the arrhythmogenic effects of newer ASMs, such as perampanel, for which current data is insufficient for comprehensive meta-analysis.[10]
- Large-scale and well-designed cohort studies are required to further confirm electrical markers and structural alterations related to the "epileptic heart" and to identify additional reliable novel indicators that could predict cardiac risk.[8]
- A more intensive understanding of the intricate brain-heart axis is necessary to fully explain the anatomical and functional connections between the brain and heart and their implications for cardiac health in epilepsy.[8]
- Continued exploration of the pathophysiological mechanisms underlying the development of the "epileptic heart" is strongly encouraged.[8]
- Future investigations should specifically focus on the three components of cardiac arrhythmia as proposed by Dr. Coumel: the substrate (e.g., controlling or reversing cardiac structural alterations), the trigger (e.g., suppressing seizure episodes), and the modulator (e.g., rectifying autonomic imbalance).[8]
- There remains an unmet need to comprehensively investigate cardiac arrhythmias in patients with epilepsy in ambulatory settings using concurrent EEG and ECG monitoring, which could provide more detailed insights into ictal and interictal cardiac events.[13]

The most pressing need is to resolve the direct contradictions concerning the cardiac

effects of specific ASMs like lacosamide and carbamazepine. This requires studies explicitly designed for head-to-head comparisons of ASMs on cardiac outcomes, ideally through randomized controlled trials, although such trials for rare adverse events can be challenging. Furthermore, detailed mechanistic studies, building upon initial work like the Langendorff model mentioned in Li et al. [22], are crucial to understand precisely why these medications exhibit divergent effects on ion channels and cardiac electrophysiology. This includes exploring how these effects translate to clinical outcomes in diverse patient populations, considering factors such as varying age groups, the presence of underlying cardiac disease, and polypharmacy. Such research is expected to lead to clearer, evidence-based guidelines for ASM selection.

The discussion of electrical alterations such as P-wave heterogeneity, T-wave alternans, and QT prolongation as potential predictors of sudden cardiac death [8] suggests a promising avenue for identifying reliable biomarkers for cardiac risk in epilepsy. Future research should focus on validating these and other potential markers, including inflammatory markers and genetic predispositions, in large, well-characterized cohorts. The ultimate goal is to develop robust predictive models that can accurately identify high-risk epilepsy patients who would most benefit from intensive cardiac monitoring or specific, tailored ASM choices, thereby enabling truly stratified care.

The recognition of the brain-heart axis [4] as a key pathophysiological mechanism implies that therapeutic interventions could target this axis directly. Beyond conventional seizure control, research could explore novel neuromodulation techniques or pharmacological agents specifically designed to normalize autonomic dysfunction in epilepsy patients, with the aim of reducing cardiac risk. This represents a new therapeutic frontier that could offer benefits beyond the primary anti-seizure effects of medications.

Specific Research Areas:

- **Comparative ASM Safety Studies:** Conduct prospective, comparative studies on the cardiac safety profiles of ASMs, particularly focusing on those with conflicting data (e.g., lacosamide, carbamazepine), to provide definitive guidance.
- **Mechanistic Elucidation:** Investigate the precise effects of ASMs on cardiac ion channels and electrophysiology, exploring how these effects vary with dosage, duration of exposure, and patient comorbidities.
- **Biomarker Discovery and Validation:** Develop and validate novel cardiac biomarkers (e.g., ECG-derived parameters, blood-based markers) for the early and accurate identification of high-risk epilepsy patients.

- **Brain-Heart Axis Interventions:** Research interventions (pharmacological, neuromodulatory) specifically targeting autonomic dysfunction to mitigate cardiac risk in epilepsy.
- **Longitudinal Studies on Newer ASMs:** Conduct long-term longitudinal studies on the cardiovascular outcomes of newer ASMs (e.g., perampanel) to gather sufficient data for comprehensive risk assessment.

VII. Conclusion

The reviewed literature unequivocally establishes epilepsy as an independent risk factor for a spectrum of cardiovascular complications, including various arrhythmias and sudden cardiac death. This phenomenon is often described by the concept of the "epileptic heart," which highlights the direct pathophysiological impact of chronic seizures on cardiac structure and function.

While anti-seizure medications are indispensable for effective seizure control, their influence on cardiac health is complex and varies significantly among individual drugs. Some ASMs, such as lacosamide and carbamazepine, present conflicting evidence regarding their arrhythmogenic potential, leading to a need for careful clinical consideration. In contrast, other ASMs like levetiracetam and lamotrigine appear to exhibit more favorable cardiac safety profiles.

These findings necessitate a paradigm shift towards integrated cardio-neurological care. This approach emphasizes proactive cardiac monitoring, personalized ASM selection based on a patient's unique cardiac risk profile, and comprehensive management of traditional cardiovascular risk factors.

Future research must prioritize resolving the existing discrepancies through robust comparative and mechanistic studies. Furthermore, efforts should focus on identifying reliable cardiac biomarkers for early risk stratification and exploring novel therapeutic strategies that specifically target the intricate brain-heart axis. Such concerted efforts are crucial to improve long-term outcomes and ultimately reduce premature mortality in individuals living with epilepsy.

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