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ACUTE CORONARY SYNDROME IN PATIENTS WITH EPILEPSY: A NARRATIVE REVIEW

Dwi Putra Haliim

Departemen Kardiologi dan Kedokteran Vaskular, Fakultas Kedokteran, Universitas Hasanuddin, Makassar

*)Email Korespondensi: dwiputrahaliim@gmail.com

Abstract: Acute Coronary Syndrome in Patients with Epilepsy: A Narrative Review. *Acute coronary syndrome (ACS) is a major public health burden with particularly high prevalence among people with epilepsy, which complicates risk stratification, management, and outcomes. This review followed the PRISMA guideline and literature search was performed on PubMed, Scopus, and Science Direct. Inclusion criteria included original research with cohort, case-control, or cross-sectional design comparing ACS prevalence in populations with and without epilepsy. A total of 936 studies were retrieved and seven studies were included in this review. All included studies had low risk of bias. Qualitative analysis of extracted data reveals that epilepsy independently increases the risk of ACS, particularly acute myocardial infarction, and is consistently associated with poorer prognosis relative to the general population. Notably, the analysis unraveled two clusters of risk factors: conventional cardiovascular risks (e.g., older age, metabolic comorbidities, atherosclerosis) and epilepsy-specific factors (e.g., epilepsy-related hospitalizations, specific antiepileptic drug regimens). The latter suggests that disease management choices may exacerbate cardiovascular vulnerability. These findings imply that current cardiovascular risk models are insufficient for epilepsy patients, and they underscore a critical need for multidisciplinary strategies that directly address epilepsy-specific challenges to improve clinical outcomes.*
Keywords: *Acute Coronary Syndrome, Epilepsy, Myocardial Infarction, Seizures*

Abstrak: Sindrom Koroner Akut pada Pasien Epilepsi: Tinjauan Naratif. Sindrom koroner akut (SKA) merupakan salah satu masalah kesehatan masyarakat yang signifikan, dengan estimasi prevalensi yang secara khusus lebih tinggi pada populasi orang-orang dengan epilepsi, yang mempersulit stratifikasi risiko, penatalaksanaan, dan luaran klinis. Tinjauan ini mengikuti pedoman PRISMA dan penelusuran literatur dilakukan pada PubMed, Scopus, dan Science Direct. Kriteria inklusi meliputi penelitian dengan desain kohort, kasus-kontrol, atau potong lintang yang membandingkan prevalensi SKA pada populasi dengan dan tanpa epilepsi. Sebanyak 936 studi didapatkan dari penelusuran literatur dan tujuh studi disertakan dalam tinjauan ini. Semua studi inklusi memiliki risiko bias rendah. Analisis kualitatif data yang diekstraksi menunjukkankan bahwa epilepsi secara independen meningkatkan risiko SKA, khususnya infark miokard akut, dan secara konsisten terkait prognosis yang lebih buruk dibandingkan populasi umum. Analisis mengungkap dua kelompok faktor risiko: risiko kardiovaskular konvensional (usia lanjut, komorbiditas metabolik, aterosklerosis) dan faktor spesifik epilepsi (rawat inap terkait epilepsi, rejimen obat antiepilepsi tertentu), menunjukkan bahwa pilihan manajemen penyakit dapat memperburuk kerentanan kardiovaskular. Temuan ini mengindikasikan bahwa model risiko kardiovaskular saat ini tidak memadai untuk pasien epilepsi, dan menggarisbawahi kebutuhan akan strategi multidisiplin yang secara langsung mengatasi tantangan spesifik epilepsi untuk meningkatkan luaran klinis.
Kata Kunci: Sindrom Koroner Akut, Epilepsi, Infark Miokard, Kejang.

INTRODUCTION

Acute Coronary Syndrome (ACS) represents a significant public health concern with considerable morbidity and mortality, being one of the leading causes of hospitalizations and deaths worldwide (Ralapanawa & Sivakanesan, 2021). The global prevalence of ACS varies significantly, with estimates suggesting that approximately 3.8% to 9.5% of adults experience myocardial infarction (MI), with varying incidence rates and risk factor profiles across populations, particularly by age, sex, and geographic region (Salari et al., 2023). The prevalence of ACS is particularly high among populations with coexisting health conditions, including those with epilepsy, which can complicate risk stratification, patient management, and outcomes (Bucci et al., 2023).

Epilepsy is a neurological disorder that is marked by recurrent seizures which affects approximately 52 million people worldwide, a majority of which (>80%) reside in low- to middle-income countries (GBD Epilepsy Collaborators, 2025). Individuals with epilepsy face multiple comorbidities, both through the direct neurological implications to multi-system implications of the disease (DeGiorgio et al., 2020; Sravanthi et al., 2021).

The cardiovascular complications of epilepsy are contributing factors to the morbidity and mortality associated with epilepsy. Studies indicate that patients with epilepsy face a significantly higher risk of sudden cardiac death, with some literature suggesting a threefold increased risk compared to the general population (Garcia de Carvalho Laguna et al., 2023). This elevated risk is important to be taken into account in clinical practice given the frequent cardiovascular comorbidities experienced by this demographic, such as hypertension and dyslipidemia, which are known contributors to ACS (Fox & Mishra, 2024).

The relationship between epilepsy and cardiovascular diseases have been studied rigorously. Autonomic dysfunction has been identified as a major factor, in which seizure activity impacts the heart's autonomic regulation, potentially precipitating arrhythmias or other cardiovascular events (Bucci et al., 2023; Stefanidou et al., 2022). Additionally, certain antiepileptic drugs (AEDs) have been implicated in influencing cardiovascular outcomes, further complicating the health conditions of these patients (M. C. H. Li et al., 2019; Nei et al., 2025). There is growing evidence suggesting a bidirectional relationship in which cardiovascular issues can exacerbate seizures, while seizures can lead to acute changes in cardiovascular stability (Surges et al., 2021).

Understanding the relationship between acute coronary syndrome and epilepsy is vital for improving management strategies and clinical outcomes. The prevalence, associated risk factors, effect of AEDs and seizures on ACS, as well as the outcome of ACS in people with epilepsy are particularly relevant in clinical practice (DeGiorgio et al., 2020; Sravanthi et al., 2021).

Several studies have independently investigated different aspects of epilepsy and its association with cardiovascular events, sudden death, and cardiac arrest. However, no reviews have been made specifically focusing on epilepsy and ACS. This review aims to systematically evaluate the risk, outcomes, and contributing factors of ACS in epilepsy patients.

METHODS

This narrative review was done by performing a comprehensive literature search in three databases: PubMed, Scopus, and Science Direct. The search was performed on August 24th, 2025 by one reviewer (DP). The literature search in this study focused on finding relevant articles on acute coronary syndrome in epilepsy patients. The search strategy used the following keywords: ("acute coronary syndrome" OR “ACS” OR "myocardial infarction" OR “MI” OR "unstable angina" OR “UAP” OR “unstable angina pectoris” OR “heart attack” OR “cardiovascular event*”) AND ("epilepsy" OR “epilept*” OR “epilept* disorder*” OR “seiz* disorder*”) AND

("cohort" OR "case-control" OR "case control" OR "cross-sectional" OR "cross sectional" OR "population-based").

The articles were collected and screened using previously established inclusion and exclusion criteria. The inclusion criteria for this literature review were original articles and other primary sources in English. The literature must be accessible in full text with no limitation on publication date. The included literature must contain information on ACS in patients with epilepsy, as well as supporting research on risk factors or drug therapies that have implications for the risk of ACS in patients with epilepsy. The types of study that can be used in this literature review include cohort studies, case-control studies, and cross-sectional studies. Articles not eligible for inclusion in this literature review include articles in the form of proceedings, theses, dissertations, and articles with titles, abstracts, and keywords that do not meet the inclusion criteria. Studies that meet one or more of these criteria were excluded from this literature review.

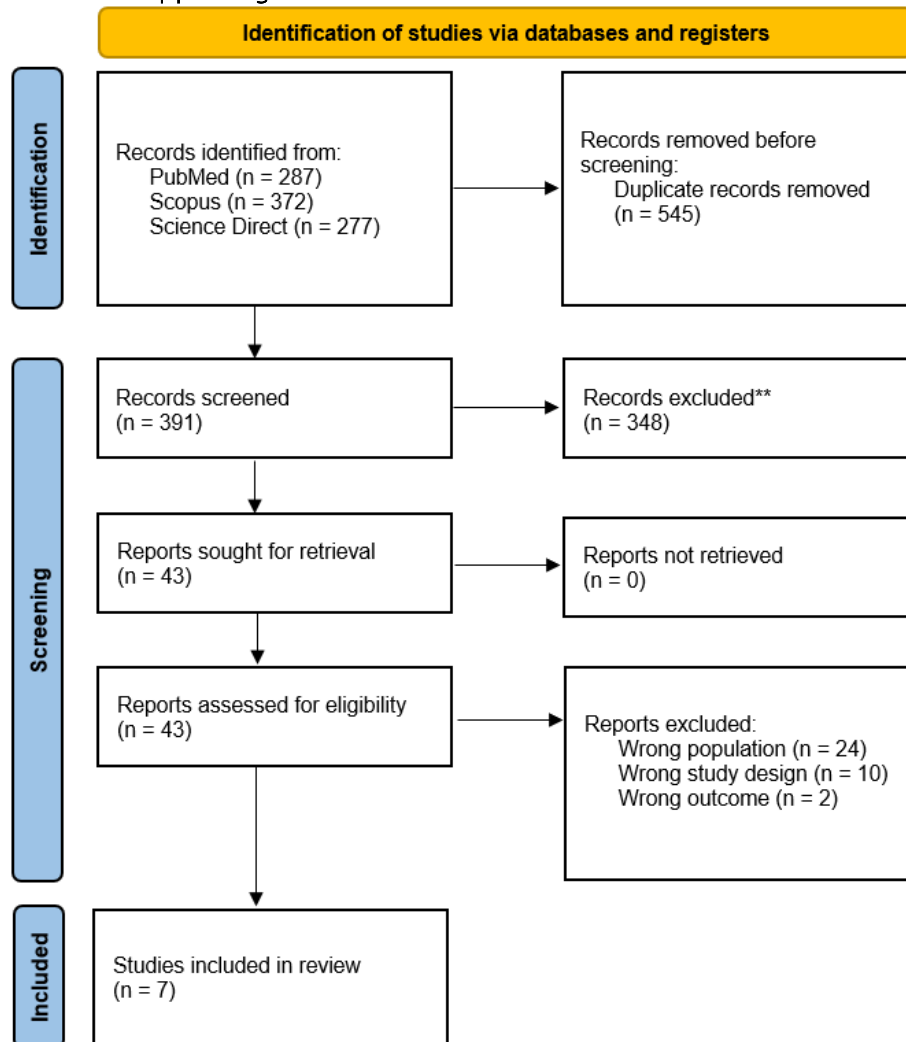

Figure 1. PRISMA Flow Diagram

Articles retrieved from literature searching were screened using a step-wise approach based on previously established inclusion and exclusion criteria. Screening was initially done based on titles and abstracts, followed by full-text screening. The final included studies were then compiled and extracted for relevant data and information. This data included author names, year of publication, design, location, research methods, and results.

Risk of bias was assessed using Newcastle-Ottawa Scale which showed

that all studies had low risk of bias for all three domains, with the exception of moderate risk of bias in four studies in the domain of selection, one in the domain of comparability, and one in the domain of outcome. The overall risk of bias for all included studies was low.

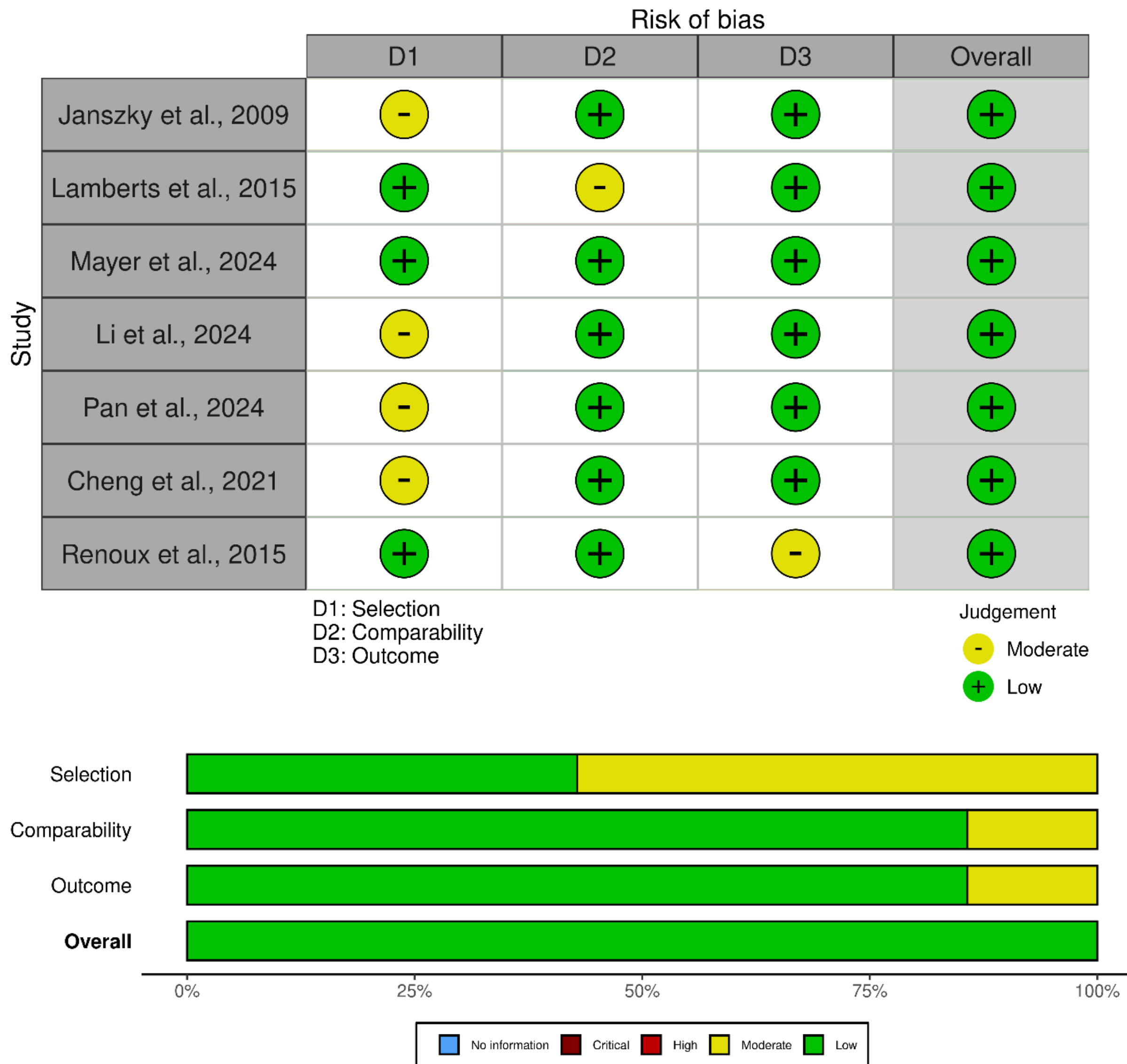

Figure 2. Risk of Bias of Included Studies

RESULTS

After literature search, a total of 936 studies were retrieved, consisting of 287 studies from PubMed, 372 studies from Scopus, and 277 studies from Science Direct. After removal of duplicates, 391 studies remained. The screening process was performed using a step-wise approach based on previously established inclusion and exclusion criteria. Screening was initially done based on titles and abstracts, resulting in 43 studies. Full-text screening was further conducted, which eliminated 36 studies. Finally, seven studies were included in this review.

Table 1. Summary table of included studies

Author, Year	Location	Study Design	Methods	Participants	Results
Janszky et al., 2009	Sweden	Case-control (with 8-year cohort follow-up)	Patients with history of epilepsy and AMI along with data about their lifestyle & biomarkers	1,799 first AMI cases and 2,339 controls, 45 of which had epilepsy	Epilepsy was associated with higher risk of AMI, OR 4.83 (95% CI: 1.62–14.43) after adjustments for clinically relevant AMI risk factors. Prognosis after AMI (8 years): Cardiac mortality HR = 3.49 (95% CI: 1.05–11.65); Total mortality HR = 1.95 (95% CI: 0.70–5.43).
Lamberts et al., 2015	Netherlands	Case control	People with epilepsy who had VT/VF and VT/VF controls were compared to epilepsy controls.	18 cases with VT/VF and epilepsy, 470 people with VT/VF without epilepsy, and 54 people with epilepsy without VT/VF.	Compared to VT/VF controls without epilepsy, patients with epilepsy had a higher risk of experiencing cardiac arrest due to AMI (HR 1.19 (CI 0.38–3.70)).
Mayer et al., 2024	France	Retrospective cross-sectional and longitudinal cohort	Hospitalized patients with epilepsy were matched with patients without epilepsy.	682,349 hospitalized epilepsy patients and 682,349 patients without epilepsy	Patients with epilepsy had higher cardiovascular death (IRR = 2.16, 95% CI = 2.11–2.20), and cardiac arrest (IRR = 2.12, 95% CI = 2.04–2.20). The incidence (IRR = 0.89, 95% CI = 0.86–0.91) and risk (SHR = 0.63, 95% CI = 0.61–0.65) of MI were lower in the

					patients without epilepsy.
Li et al., 2024	Canada	Prospective cohort	Data obtained from Canadian Longitudinal Study on Aging. Mediation analyses were conducted. The use of strong enzyme-inducing anti-seizure medication (EIASM), weak EIASM use, and the Framingham score data were obtained.	27,230 individuals, 431 of which had a history of epilepsy	The odds of new-onset CVEs and MIs were significantly higher in people with vs without epilepsy (OR for any CVE, 2.20; 95% CI, 1.48-3.27, OR for new-onset MIs 1.85 (1.04-3.27)). The effect proportion of epilepsy on new-onset cardiovascular events mediated by strong EIASM use was 24.6% (95% CI, 6.5%-54.6%) and 59.1% (26.3 to 126.9) for MI.
Pan et al., 2024	United States	Retrospective cohort	Analysis on inpatients diagnosed with epilepsy, including those with or without AMI were performed. Data were analyzed for temporal trends, outcomes, and risk factors of AMI in PWE.	8,456,098 adults diagnosed with epilepsy were included, of which 181,826 (2.15%) had concomitant AMI.	AMI prevalence in PWE increased from 1,911.7 to 2,529.5 per 100,000 hospitalizations between 2008 and 2017. In-patient mortality was higher in PWE with AMI (13.35%) compared to those without (2.5%). AMI was associated with increased in-patient mortality (OR = 4.61, 95% CI: 4.54 to 4.69) and other complications. Risk factors associated with AMI in PWE included being ≥75 years old (OR = 3.54), atherosclerosis (OR = 4.44),

					conduction disorders (OR = 2.21), and cardiomyopathy (OR = 2.11).
Cheng et al., 2021	Taiwan	Cohort	Data obtained between 1997 and 2013 was obtained, with a cohort of patients diagnosed with epilepsy who were free of prior cardiac diseases, and matched with a non-epilepsy cohort. The development of myocardial infarction (MI), arrhythmia, and sudden death were analyzed.	5,411 people with epilepsy and 21,644 people without epilepsy	The epilepsy group had significantly higher risks for development of MI (HR = 1.71; 95% CI, 1.62–1.81; P < 0.001) and sudden death (HR = 1.83; 95% CI, 1.53–2.18; P < 0.001) compared to people without epilepsy. The epilepsy cohort had higher rates of comorbidities like hypertension, cerebrovascular disease, and diabetes mellitus.
Renoux et al., 2015	United Kingdom (UK)	Case-control	Data was obtained from 650 UK general practices (CPRD). Sample of incident AED users aged 18 or older was obtained. Matched cases and controls (up to 10 per case) based on age, sex, AED indication, calendar time, and follow-up duration. AEDs were categorized as enzyme-inducing, inhibiting, or non-inducing. Incidence of myocardial	252,407 incident AED users.	Prolonged use of EIASM showed a slight increase in MI. Inhibiting AEDs use was associated with decreased risk of MI. The overall incidence rate for AMI was 3.63 (95% CI 3.51 to 3.75) per 1000 persons per year.

		infarction was identified from medical records.	

Of the seven included studies, two were case-control studies, three were cross-sectional, and two were cohort studies. Four studies were based on multicenter, nationwide databases while three studies analyzed data from single-center databases. Four studies focused on patients with a history of epilepsy, one focused on the history of AEDs use, and one study focused on patients with a history of epilepsy and arrythmia.

ACS Prevalence and Risk in Epilepsy Patients

Six studies analyzed the risk and prevalence of ACS in epilepsy patients and came to similar conclusions that there is an increased risk of ACS in this population. Mayer et al. analyzed data from national databases with a total of 1,364,698 patients and concluded that there was a lower incidence (IRR = 0.89, 95% CI = 0.86–0.91) and risk (SHR = 0.63, 95% CI = 0.61–0.65) for myocardial infarction (MI) in people without epilepsy compared to people with epilepsy (Mayer et al., 2024). Li et al. had similar findings, in which there was a significantly lower incidence and risk of MI in the group of people without epilepsy compared to the group of people with epilepsy (J. Li et al., 2024).

Similarly, analysis from 4,138 patients from the Swedish hospital discharge registry found higher risk of acute MI in patients with epilepsy compared to control with an OR of 4.83 after adjustment for demographics and clinically relevant AMI risk factors (Janszky et al., 2009). Cheng et al. found significantly higher risks for MI in people with epilepsy (HR = 1.71) (Cheng et al., 2021). In the specific population of people with epilepsy (PWE), the overall incidence rate for AMI was 3.63 per 1000 persons per year (Renoux et al., 2015). Pan et al. conducted a study involving 8,456,098 PWE from 2008 to 2017 and found increased prevalence of AMI from 1,911.7 per 100,000 hospitalizations in 2008 to 2,529.5 per 100,000 hospitalizations in 2017 (Pan et al., 2024).

Exacerbating Risk Factors for ACS in Epilepsy Patients

Two studies identified risk factors associated with ACS in epilepsy patients. Pan et al. found that risk factors for AMI in PWE included age ≥75 years (OR = 3.54), atherosclerosis (OR = 4.44), conduction disorders (OR = 2.21), and cardiomyopathy (OR = 2.11) (Pan et al., 2024). Janszky et al. found a graded positive relation between number of hospitalizations for epilepsy and AMI risk (Janszky et al., 2009).

Anti-Epileptic Drugs

Two studies focused on the use of AEDs and found slightly different results. Li et al. found the proportion of the effect of epilepsy on new-onset CVEs being mediated by strong enzyme-inducing anti-seizure medication (EIASM) use was 24.6% and 59.1% for MI (J. Li et al., 2024).

Conversely, Renoux et al. found that current inducing AED use had no significant association with MI risk. However, it more specifically found that current use of enzyme-inducing AED for more than 24 months had significant association with MI (RR 1.46) compared to the same duration of non-inducing AED use (Renoux et al., 2015).

Outcomes and Mortality

Two cohort studies focused on the population of PWE with MI and found similar results. Pan et al. found that inpatient mortality was higher in PWE who also experience MI (13.35%) compared to PWE without MI (2.5%). MI had significant association with inpatient mortality and other complications (Pan et al., 2024). Janszky et al. found that the 8-year prognosis after AMI revealed worse cardiac mortality and total mortality for PWE (Janszky et al., 2009).

On the other hand, Lamberts et al. focused on patients with arrythmia and found that compared to VT/VF controls without epilepsy, patients with epilepsy

had a higher risk of experiencing cardiac arrest due to AMI (HR 1.19) (Lamberts et al., 2015).

DISCUSSION

Acute Coronary Syndrome (ACS) poses significant health risks to patients with epilepsy. All studies in this review that assessed the risk for ACS, specifically MI, found a higher risk for people with epilepsy compared to people without epilepsy, after adjusting for demographics and clinical risk factors (Cheng et al., 2021; Janszky et al., 2009; J. Li et al., 2024; Mayer et al., 2024; Pan et al., 2024; Renoux et al., 2015). This finding is in line with the Stockholm Heart Epidemiology Program, which demonstrated that patients hospitalized for epilepsy had a greater likelihood of experiencing myocardial infarctions (Fayaz et al., 2024).

Several factors may explain the higher risk of ACS for people with epilepsy. Notably, the prevalence of several cardiovascular comorbidities in epilepsy patients significantly heightens the risk of experiencing ACS. Individuals with epilepsy face a higher burden of cardiovascular risk factors, including hypertension, dyslipidemia, and lifestyle factors such as smoking (Husein et al., 2021; Markoula et al., 2022; Pan et al., 2024).

A study on 501,896 people with and without epilepsy from the UK Biobank found that hypertension, coronary artery disease, heart failure, and valvular heart disease were more prevalent in people with epilepsy compared to people without epilepsy (Shah et al., 2024). In population-based cohorts, researchers have documented that epilepsy can exacerbate cardiovascular morbidity and mortality, aligning with findings from this review that illustrate rising incidence of ACS in the epilepsy population compared to controls. Some studies highlighted biochemical markers like homocysteine and coagulation factors as mediators of increased risk in epilepsy (Gaertner et al., 2024; Janszky et al., 2009).These factors exacerbate the risk for developing ACS as well as worsen the clinical outcomes of ACS (Trinka et al., 2013)

In addition, epilepsy-specific factors including enzyme-inducing antiseizure medications and seizure-related autonomic dysfunction contribute to cardiovascular risk, the cumulative impact of which cannot be overlooked (Lee-Lane et al., 2021). Various AEDs have been implicated in the exacerbation of pre-existing cardiovascular conditions, and medication-related side effects can significantly impact lipid metabolism and endothelial function, leading to increased atherosclerotic changes (Markoula et al., 2022).

The use of several AEDs, particularly enzyme-inducing medications, can adversely alter lipid profiles and glucose metabolism (Lamberts et al., 2015; Markoula et al., 2022). The Canadian Longitudinal Study on Aging provided insights into how these medications correlated with higher incident cardiovascular events, raising concerns about their long-term cardiovascular impacts (J. Li et al., 2024). Enzyme-inducing antiseizure medications are associated with increased cardiovascular risk and incident events in a dose-dependent manner (Josephson et al., 2021; J. Li et al., 2024; Renoux et al., 2015; Vossler, 2022). However, some studies found no significant difference in cardiovascular event risk between enzyme-inducing and non-inducing AEDs, indicating complexity in drug effects (Lee-Lane et al., 2021). The role of AEDs in modulating cardiovascular risk therefore remains an important area for further research.

The interplay between cardiovascular risk factors, potential side effects of some AEDs, and the pathophysiology of epilepsy creates a complex landscape for managing heart health in these patients. Numerous studies have reported higher all-cause and cardiovascular mortality in epilepsy patients following acute coronary events, with odds ratios and hazard ratios often exceeding 2.0 (Fayaz et al., 2024; Mayer et al., 2024; Pan et al., 2024; Shah et

al., 2024). PWE are more likely to suffer sudden-death events, as well as having a higher incidence of all-cause death, cardiovascular death, and cardiac arrest (Shah et al., 2024). Cheng et al. also found that PWE have significantly higher risks for sudden death (Cheng et al., 2021). A community-based study explored the relationship between seizure episodes and sudden cardiac arrest occurrences in patients and found PWE to have worse survival outcome in sudden cardiac arrest (Stecker et al., 2013).

The relationship between epilepsy and ACS is multifactorial and involves a complex interplay of autonomic nervous system dysfunction, genetic susceptibility, and seizure- or medication-induced cardiac structural and electrophysiological changes (Gigli et al., 2023; Gonca et al., 2018). Autonomic imbalance, as characterized by sympathetic overactivity and impaired parasympathetic regulation, emerges as a central mechanism that disrupts the normal cardiac response to stress and potentially contributes to myocardial ischemia, arrhythmogenesis, and cardiac remodeling (Senapati et al., 2023). Autonomic dysfunction is frequently observed in epilepsy patients, leading to changes in heart rate variability and cardiovascular responsiveness during seizures (Trinka et al., 2013).

Furthermore, seizures can negatively impact the prognosis of ACS by exacerbating myocardial injury, increasing arrhythmia incidence, and elevating in-hospital mortality rates. Experimental and clinical data illustrate that seizure activity intensifies ischemic myocardial damage and rhythm disturbances, potentially through autonomic and neurogenic mechanisms (Fialho et al., 2018; Gonca et al., 2018). Studies using myocardial perfusion imaging illustrate that epileptic patients often exhibit silent myocardial ischemia, indicating underlying cardiovascular changes that may not present with overt symptoms (Fayaz et al., 2024).

Seizures precipitate acute catecholamine surges, hypoxemia, and transient myocardial injury, which can manifest clinically as seizure-associated myocardial infarction, arrhythmias, and stress-induced cardiomyopathies such as Takotsubo syndrome. Shared genetic and ion channel pathologies further compound this risk, linking cerebral and cardiac electrophysiological vulnerabilities (Nandal et al., 2019; Senapati et al., 2023). There have been documented cases in which ictal episodes led to immediate cardiac complications, including myocardial ischemia and ventricular fibrillation during seizures (Camacho Velásquez et al., 2017; Mously et al., 2018). The acute physiological stress induced by seizures can lead to increased sympathetic activity, which can precipitate ACS (Stecker et al., 2013). These findings underline the need for vigilant cardiovascular monitoring in patients with uncontrolled epilepsy or frequent seizure episodes.

Conversely, acute coronary pathology can influence seizure dynamics, although fewer studies have directly addressed the reciprocal effect of ACS on seizure frequency or severity. However, some evidence suggests that coronary artery disease may increase epilepsy risk, particularly in individuals with low genetic susceptibility (Zhang et al., 2025). Cases of ictal asystole related to coronary stenosis indicate that cardiac ischemia can influence seizure manifestations and severity (Fortunato et al., 2021). However, this reciprocal relationship is less thoroughly studied and warrants further prospective investigation.

This review included studies that analyzed multiple muti-center nationwide databases with large pool of patients and long follow-up duration. However, these studies have the limitation of analyzing secondary data from databases and medical records, with higher potential for unaccountable provider- or patient-related factors for which the study investigators had little to no ability to control (i.e. treatment adherence, other clinical factors influencing medical decision-making, and lifestyle factors not properly

documented or followed-up) and might confound the results and analysis.

However, the qualitative analysis from this review reveals several important clinical implications. The higher prevalence and risk of ACS in epilepsy patients along with different complexity of physiological, pharmacological, and lifestyle factors, emphasize the necessity for a multidisciplinary approach in managing patients with epilepsy. The comorbidity of epilepsy and ACS should not be treated as independent, separate medical conditions. Instead, they should be understood as interconnected conditions that affect one another in multiple ways. Medical providers involved in the care of individuals with epilepsy should have this understanding and employ clear and continuous communication with other providers to ensure comprehensive and holistic management to improve cardiovascular health outcomes.

CONCLUSION

People with epilepsy (PWE) have a markedly increased risk for Acute Coronary Syndrome (ACS), which is aggravated by several cardiovascular risk factors, including hypertension, dyslipidemia, lifestyle factors, and the use of some anti-epileptic drugs (AEDs). Notably, enzyme-inducing AEDs have been identified as potential contributors to increased cardiovascular event risks. PWE have worse outcomes for acute myocardial infarction and for all-cause mortality compared to the general population. This review underscores the significance of cardiovascular prevention and management in PWE. A multidisciplinary approach that acknowledges the unique challenges in epilepsy patients is crucial in improving clinical outcomes.

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