Acquired Epilepsy with a Focus on Stroke

Treatment and Prognosis

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ABSTRACT

The relationship between epilepsy and stroke is complicated. While stroke is a major cause of epilepsy after middle age, there is also evidence that the risk of stroke is increased in persons with epilepsy. The overall aim of this dissertation is to elaborate on the prognosis and treatment of epilepsy in older adults and its association to stroke. It is based on four studies which have been conducted using information from linked national registers, which offer unique opportunities to follow thousands of patients over a long period of time.

The results from Papers I-II indicate that a significant proportion of all new-onset seizures after middle age will herald a subsequent stroke. Using incidence data and population statistics, we estimated the 10-year risk of stroke to be between 5-20%, depending on age group. In relative terms, the risk appears to be almost two-fold (odds ratio [OR] 1.77; 95% confidence interval [95%CI] 1.65-1.89) compared with age-matched controls from the general population – and highest during the first year after seizure onset (OR 2.21; 95 % CI 1.79–2.72).

The studies described in Papers III-IV examined prognostic aspects of antiseizure medication (ASM) therapy in poststroke epilepsy. Paper III found the 5-year retention rate to be highest for lamotrigine (0.75, 95%CI 0.70–0.79) and levetiracetam (0.69, 95%CI 0.63–0.74), suggesting these drugs are well tolerated in this patient group. Paper IV used a similar methodology but investigated if mortality varied with different ASMs in monotherapy. Patients treated with lamotrigine had lower mortality (hazard ratio [HR] 0.72, 95%CI 0.60-0.86) than the reference group treated with carbamazepine, while patients treated with valproic acid had higher mortality (HR 1.40, 95%CI 1.23-1.59). Treatment with levetiracetam was associated with a reduced risk of cardiovascular death compared to carbamazepine (HR 0.77, 95%CI 0.60-0.99).

In conclusion, this thesis supports a tailored management approach in adults with new-onset seizures late in life, particularly in those with a history of stroke. Persons with late-onset seizures have high vascular risk, potentially warranting screening and treatment for vascular risk factors. Moreover, the association between ASM selection and mortality raises concerns about clinically relevant drug-drug or drug-disease interactions that may modify vascular risk. Overall, lamotrigine and levetiracetam seem sensible initial treatment options in this patient group.

SAMMANFATTNING

Stroke är den vanligaste identifierbara orsaken till epilepsi. Trots det är kunskapen om behandling begränsad, till stor del på grund av svårigheter att följa äldre, multisjuka patienter över tid. Epilepsiläkemedel har olika biverkningar, men om något läkemedel är bättre tolererat än andra vid epilepsi efter stroke är sparsamt undersökt. De riktlinjer som finns baseras huvudsakligen på studier där man inte har tagit hänsyn till underliggande samsjuklighet.

Nyligen konstaterades även att epilepsi efter stroke ökar risken för död. Riskökningen kan inte förklaras av epileptiska anfall – istället utgör hjärt-kärlsjukdom den dominerande dödsorsaken. Flera vanliga epilepsiläkemedel interagerar med läkemedel som minskar risken för återinsjuknande i stroke, men om valet av epilepsiläkemedel vid epilepsi efter stroke påverkar överlevnaden är okänt.

Ytterligare en intressant – och bekymmersam – aspekt är att även det omvända förhållandet verkar råda, det vill säga att personer med epilepsi löper ökad risk att drabbas av stroke. Man tar i dagsläget inte hänsyn till detta vid utredning för epileptiska anfall, men flera erkända epilepsiforskare har frågat sig om inte äldre personer som drabbas av epileptiska anfall borde genomgå utredning för riskfaktorer associerade med hjärt-kärlsjukdom.

Med grund i ovanstående bygger denna avhandling på fyra delstudier som undersöker relationen mellan epilepsi och stroke respektive behandling av epilepsi efter stroke. Studierna har gemensamt att de använder information från flera samkörda nationella register, vilka erbjuder unika möjligheter att över lång tid och med hög detaljgrad följa tusentals patienter.

Resultaten pekar på att en betydande andel av alla personer med ett första epileptiskt anfall efter medelåldern senare kommer att få stroke. Med hjälp av incidensdata och befolkningsstatistik har vi uppskattat 10-årsrisken för stroke till mellan 5-20%, beroende på åldersgrupp. I relativa termer förefaller risken vara nästan dubbelt så hög jämfört med övriga befolkningen – och som allra högst under första året efter anfallsdebuten. Förebyggande behandling av riskfaktorer för stroke skulle därmed kunna motiveras, men ytterligare forskning behövs för att klargöra om nyttan med sådan behandling överväger eventuella risker och kostnader.

Beträffande behandling vid epilepsi efter stroke så talar resultaten för att livslängden och benägenheten att kvarstå på behandling varierar med vilket epilepsiläkemedel man blir förskriven, även efter att hänsyn tagits till olika bakgrundsfaktorer. Nyare och mindre interaktionsbenägna epilepsiläkemedel var generellt kopplade till bättre prognos, vilket var i linje med våra förväntningar. När vi undersökte förändringar i förskrivningsmönstret över tid kunde vi konstatera att de modernare alternativen allt oftare förskrivs som förstahandsval vid epilepsi efter stroke.

Ett av de viktigaste budskapen i denna avhandling är att personer med ett första epileptiskt anfall efter medelåldern har ökad risk för hjärt-kärlsjukdom. Detta borde särskilt gälla personer som redan tidigare har konstaterad samsjuklighet, såsom vid epilepsi efter stroke. Att risken för död varierar med behandlingsval är oroande och tyder på att äldre epilepsiläkemedel möjligen kan påverka risken för hjärt-kärlhändelser, antingen genom biverkningar eller interaktioner med andra läkemedel. Oavsett orsak bör behandlande läkare sträva efter att minimera risken för negativa effekter av behandling.

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Zelano J, **Larsson D**, Kumlien E, Åsberg S.

Pre-stroke seizures: A nationwide register-based investigation.

Seizure 2017; 49: 25-9.

II. **Larsson D**, Farahmand B, Åsberg S, Zelano J.

Risk of stroke after new-onset seizures.

Seizure 2020; 83: 76-82.

III. **Larsson D**, Åsberg S, Kumlien E, Zelano J.

Retention rate of first antiepileptic drug in poststroke epilepsy: A nationwide study.

Seizure 2019; 64: 29-33.

IV. **Larsson D**, Baftiu A, Johannessen Landmark C, von Euler M, Kumlien E, Åsberg S, Zelano J.

Association between antiseizure drug monotherapy and mortality for patients with poststroke epilepsy.

JAMA Neurology 2021; e-pub.

DOI: 10.1001/jamaneurol.2021.4584

CONTENT

ABBREVIATIONS

ADL	Activities of Daily Living
AIS	Acute Ischemic Stroke
ARIC	Atherosclerosis Risk in Communities
ASM	Antiseizure Medication
ATC	Anatomical Therapeutic Chemical Classification
CDR	The Cause of Death Register
CI	Confidence Interval
CT	Computerized Tomography
HDL	High-Density Lipoprotein
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	Intracerebral Hemorrhage
INR	International Normalised Ratio
IV	Intravenous
LDL	Low-Density Lipoprotein
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NPR	The National Patient Register
OR	Odds Ratio
PET	Positron Emission Tomography

PSE	Poststroke Epilepsy
RCT	Randomized Controlled Trial
SIRE	Stockholm Incidence Registry of Epilepsy
SPDR	The Swedish Prescribed Drug Register

1 INTRODUCTION

Epilepsy is a common disorder of the brain, found in all parts of the world and all age groups. It is characterized by an enduring predisposition to generate epileptic seizures.[1] The diagnosis of epilepsy usually requires the occurrence of at least two unprovoked seizures more than 24 hours apart. Still, it is possible to diagnose epilepsy after a single unprovoked seizure if the physician identifies a predisposing cause associated with a high recurrence risk, stroke being a case in point.[2]

In all forms of epilepsy, the initial goal of pharmacological treatment is complete seizure freedom in the absence of adverse effects. The treatment of older adults poses a particular challenge. Age-related physiologic changes influence the pharmacokinetics and pharmacodynamics of antiseizure medications (ASMs), supporting the use of a 'start low, go slow' approach, and possibly also lower target doses.[3] Moreover, the presence of comorbidities and related therapies may result in clinically relevant drug-disease and drug-drug interactions.

The incidence of epilepsy and unprovoked seizures in high-income countries increases substantially after middle age and peaks in the elderly.[4-6] The distribution reflects a parallel increase in aging-related structural causes, with stroke, neurodegenerative disorders, intracranial tumours, and traumatic brain injuries being most common. In one-third to half of all cases, no apparent cause is found.[6-8] Although there may be similarities between epilepsies of different etiologies, there is no doubt that other factors, such as demographics and comorbidities, can differ and influence management. As a result, etiologic subgroups have received more attention in recent years, which is part of a broader trend to customize healthcare, with decisions and treatments tailored to each individual. As of yet, there are no official epilepsy treatment guidelines stratified by etiology, but some organizations provide recommendations specifically for older adults with focal epilepsy.

Even when the cause is unknown, acquired epilepsy in adults is often presumed to arise from an unspecified structural abnormality. Accordingly, unexplained epilepsy should be considered a heterogeneous entity, encompassing various undetermined causes. In some individuals, the processes involved in the normal or "healthy" aging of the brain may be responsible; in others, new-

onset seizures might be the first sign of an underlying neurodegenerative or cerebrovascular disorder. In light of this, it has been argued that older adults with new-onset seizures should be screened for the presence of vascular risk factors and cognitive impairment.

The focus of this thesis is to elaborate on treatment and prognosis in adults with an onset of epilepsy late in life, with a particular focus on cerebrovascular disease. The first part investigates whether late-onset epilepsy should be considered a marker for increased vascular risk in general, and a risk factor for subsequent stroke in particular. The second part discusses the management and treatment of persons with poststroke epilepsy, a vulnerable group with high vascular risk and specific drug–drug interaction issues related to stroke prevention. It remains to be seen how persons with late-onset seizures are best managed and what impact ASMs have on prognosis and vascular-risk profile.

2 OUTLINE

This dissertation investigates the bidirectional relationship between stroke and epilepsy, focusing on prognosis and treatment, and has the following outline:

- **Knowledge Gaps and Objectives** briefly summarizes why the included studies were conducted in the first place.

- **Seizures as a Warning Sign for Stroke** presents Papers I-II and reviews the available evidence for associations between epilepsy and subsequent stroke.

- **Seizures and Epilepsy after Stroke** presents Papers III-IV, gives a brief overview of the poststroke epilepsy field, and reviews available evidence for ASM selection in poststroke epilepsy.

- **Methodological considerations** discusses the strengths and limitations of register-based research and focuses on issues specific to Papers I-IV.

- **Conclusions and future directions** summarizes the key points of the dissertation and provides suggestions for future research.

3 KNOWLEDGE GAPS AND OBJECTIVES

Paper	Knowledge gaps	Objective
I	There are uncertainties about how often seizures precede stroke. The available evidence comes from small stroke cohorts (by today's standards).	To estimate how often epileptic seizures precede stroke on a national level.
II	Case series have described a close temporal relationship between epilepsy and subsequent stroke, but the association has not been investigated further. Only two studies (both using the same data source from Taiwan) have investigated the risk of stroke stratified by stroke subtype.	To investigate the risk of stroke after seizures, stratified by age, stroke subtype, and time between seizure onset and stroke.
III	Evidence to guide ASM selection in poststroke epilepsy is scarce. Two small (underpowered) RCTs have indicated that levetiracetam and lamotrigine are better tolerated than carbamazepine. There are no previous real-world data on long-term retention rates or treatment patterns in poststroke epilepsy.	To describe treatment patterns in poststroke epilepsy and investigate the risk of treatment failure after the initiation of ASM monotherapy.
IV	Persons with poststroke epilepsy have increased mortality. Some ASMs may affect vascular risk. No studies have investigated mortality in poststroke epilepsy stratified by ASM treatment.	To investigate if the choice of ASM monotherapy is associated with cardiovascular or all-cause death.

4 SEIZURES AS A WARNING SIGN FOR STROKE

Epilepsy is well recognized to occur after a clinical stroke.[6] Several investigators have also reported an inverse relationship: epilepsy as a precursor of stroke.[9-11] To date, the mechanism for the inverse association is undetermined, but theories suggest that late-onset epilepsy may reflect underlying 'silent' cerebrovascular disease[9,12], increase isolation and sedentary behavior, or lead to treatment with ASMs that, in turn, could influence the risk of vascular events.[13]

Suppose persons with otherwise unexplained epilepsy after a certain age are at an increased risk of stroke. In that case, it may have clinical implications, as new-onset seizures could provide a window of opportunity to reduce long-term morbidity and mortality. Possible measures to reduce vascular risk include lifestyle changes, pharmacological treatment of risk factors, and tailored ASM therapy, but whether the onset of unprovoked seizures or epilepsy warrants such efforts remains unclear.

! The sub-chapter **Quantifying the risk of stroke in persons with late-onset epilepsy or seizures** presents Papers I-II

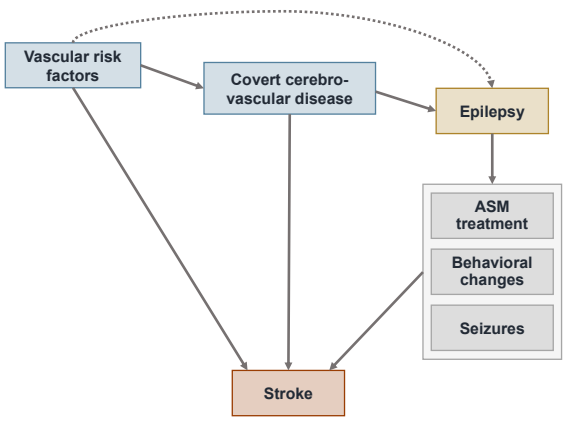


Figure 1. *Possible mechanisms of association between epilepsy and subsequent stroke. The dotted line illustrates that there might be a direct association between hypertension and epilepsy.*

VASCULAR PREDICTORS OF EPILEPSY

Vascular risk factors may affect the risk of epilepsy through direct mechanisms or by predisposing individuals to cerebrovascular disease. Large population-based studies of cross-sectional design have reported that stroke, hypertension, diabetes mellitus, and several types of heart conditions are overrepresented among persons with epilepsy.[14-16] This section assesses the evidence for associations between vascular risk factors and incident epilepsy in the absence of clinical stroke.

Hypertension explains about 35% of the risk of stroke worldwide.[17] Multiple studies have also demonstrated independent associations between hypertension and incident epilepsy. An early example is a case-control study conducted in the 1980s, which reported an OR of 1.57.[18] Recent large community-based cohort studies have corroborated that finding, linking hypertension with significantly increased HRs of late-onset epilepsy (1.30 [95%CI 1.09-1.55] and 1.93 [95%CI 1.10–3.37]).[19,20] In a sub-analysis of the Framingham Heart Study, the risk increased even further when participants with controlled hypertension were excluded (HR 2.44 [95%CI 1.36-5.35]).[20]

Some evidence from rodent models indicates that the renin-angiotensin system may be involved in seizure susceptibility. Repetitive seizures in Wistar audiogenic rats have been associated with an increased expression of angiotensin II type 1 receptors and angiotensin-converting enzyme in the brain.[21] Moreover, administration of enalapril and losartan seem to reduce seizure frequency in rat models.[21-23] While the mechanisms are poorly understood, the evidence suggests that hypertension may have an effect on epilepsy beyond the association with cerebrovascular disease.

The results regarding other possible vascular predictors are less consistent. A case-control study, conducted as part of the larger population-based Rotterdam Study, found that total cholesterol and left ventricular hypertrophy were associated with increased ORs of epilepsy (1.3 per mmol/L increase [95%CI 1.0-1.6] and 2.9 [95%CI 1.0-8.6], respectively).[24] Interestingly, ORs increased when the analyses were restricted to late-onset cases (compared with lifetime epilepsy), indicating that cardiovascular comorbidities may be of particular relevance for epilepsy that develops later in life.

In the large Atherosclerosis Risk in Communities (ARIC) study, the following variables were independently associated with increased hazard ratios (95%CI) of epilepsy: hypertension (1.30, 1.09-1.55), diabetes (1.45, 1.17-1.80), smoking (per 20 pack-years; 1.09, 1.01-1.17), apolipoprotein E4 genotype (1 allele, 1.22, 1.02-1.45; 2 alleles, 1.95, 1.35-2.81), incident stroke (3.38, 2.78-4.10), and dementia (2.56, 2.11-3.12).[19] Exercise and moderate alcohol intake were associated with a reduced risk for epilepsy.

Data from the Cardiovascular Health Study did not show any significant associations between the above vascular risk factors and incident epilepsy.[25] Surprisingly, a history of coronary heart disease, obesity and incident congestive heart failure resulted in a reduced risk. It is difficult to come up with a plausible explanation for this finding, but the authors suggest that being overweight may be neuroprotective in some individuals (the "obesity" paradox[26]). The confidence intervals were generally quite wide (example: hypertension, HR 1.33, 95%CI 0.83-2.11), suggesting the sample may have been too small to detect all relevant differences.

Moreover, case-control studies have associated statin use with a reduced risk of epilepsy (OR 0.65 [95%CI 0.56-0.75] and 0.65 [95%CI 0.46– 0.92]).[27,28] This could be due to effects of statins on vasculature, including plaque stabilization, but a healthy user effect is another possible explanation. Patients who receive one preventive therapy may be more cautious about their health, more prone to receive other preventive therapies, or have better access to healthcare services. A possible reduction in the risk of seizures from statins have also been suggested from rodent studies and some observational studies of patients with new-onset brain insults, particularly in the acute phase.[29-31]

EVIDENCE FROM NEUROIMAGING STUDIES

Cerebrovascular disease can be silent or indistinct in its manifestations. Before the advent of computerized tomography (CT) imaging in the 1970s, studies on cerebrovascular disease were limited mainly to patients with clinical stroke or other systemic vascular disorders (used as markers for assumed concomitant cerebrovascular disease). The radiological advances during the 1970s and 1980s increased detection of subclinical ('covert') cerebrovascular lesions and made it possible to obtain images from healthy controls, as non-invasive techniques were significantly less risky.

Since then, several studies have demonstrated that covert cerebrovascular disease is overrepresented among persons with epilepsy. An early CT imaging study found evidence of cerebral infarctions in 11% of cases with late-onset epilepsy compared with 2% of controls, a difference significant at the 0.003 level.[32,33] More recent studies have associated late-onset epilepsy with subclinical large vessel infarcts (OR 7.63 [95%CI 1.66–35.06]),[34] small vessel disease (OR 2.23 [95%CI 1.25–3.97]),[34] higher white matter hyperintensities burden (HR 1.28 per age-adjusted z score [95%CI 1.06-1.54]),[35] lower cortical volume,[35,36] and delayed baseline whole brain arterial arrival time.[36]

The mechanisms of epileptogenesis in cerebrovascular disease are poorly understood. This is especially true for white matter disease, since seizures are usually expected to originate from the cortex. Covert cerebrovascular disease encompasses a heterogenous group of pathologies, ranging from subclinical embolic infarcts to arteriolosclerosis and cerebral amyloid angiopathy. Even when the underlying cause can be established, the course is usually progressive, leading to a wide array of primary and secondary pathological processes which could cause neurons to become hyperexcitable.

There have been suggestions that temporal lobe networks could be susceptible to damage from white matter disease,[37] but the prevailing view is that white matter disease is a marker for co-existing cortical disease. Cortical microinfarcts are common in older adults[38] and have been associated with lacunes, white matter hyperintensities, and microbleeds.[39] Increased burden of white matter lesions has also been correlated to a higher degree of cortical atrophy.[40] In a PET study, subjects with late-onset seizures and CT-verified leukoaraiosis had decreased oxygen consumption and regional blood flow in cortical areas compared with controls.[41]

Covert cerebrovascular disease increases the risk of future stroke, cognitive decline, and death independent of systemic vascular risk factors.[42,43] In light of the findings described above, it is intuitive that covert cerebrovascular disease also influences health outcomes in persons with late-onset epilepsy. Still, there is little consensus on when and how to act on incidentally detected vascular lesions.[44] This is partly due to the heterogeneous use of imaging sequences and grading scales, which complicates comparisons between studies. Eventually, it may be possible to identify prognostic thresholds, which could be used to tailor management in late-onset epilepsy.

ANTI-SEIZURE MEDICATION SELECTION WITH REGARD TO VASCULAR RISK

Many factors contribute to determining the ASM of choice, but with advancing age, the pharmacological profile of the ASM and the propensity for drug-drug interactions become increasingly important. In the context of cardiovascular risk, the relevant drug-drug interactions are of pharmacokinetic nature. First-generation ASMs, particularly the strong liver enzyme inducers (carbamazepine, phenytoin, phenobarbital, primidone), are more prone to affect medications used to prevent cardiovascular diseases.

DRUG-DRUG INTERACTIONS

Drug-drug interactions caused by enzyme-inducing ASMs can be predicted based on their isoenzyme targets.[45] For example, carbamazepine and phenytoin are potent inducers of cytochrome P450 3A4, which mediates the metabolism of many calcium channel blockers (e.g., felodipine, amlodipine, and verapamil) and statins (e.g., simvastatin and atorvastatin).[46,47] Clinically significant interactions have been demonstrated between enzyme-inducing ASMs and simvastatin, atorvastatin, and warfarin, respectively.[46,48-50] Other drugs theorized to be affected include β-adrenergic blocking agents (e.g., metoprolol and propranolol) and non-vitamin K antagonist oral anticoagulants (NOACs). The prescribing information for apixaban, dabigatran, and rivaroxaban advise against coadministration with carbamazepine and phenytoin.[51-53]

Valproic acid is a highly protein-bound enzyme inhibitor that can increase serum concentrations of other drugs metabolized by the liver. Case reports suggest that valproic acid combined with warfarin may increase the international normalized ratio (INR), but other than that, there are no documented interactions with cardiovascular drugs.[54-56]

Second-generation ASMs are generally less likely to produce pharmacokinetic interactions. In a study of seven healthy subjects, felodipine mean exposure decreased after repeated doses of oxcarbazepine.[57] Moreover, eslicarbazepine acetate can reduce the exposure of statins and warfarin.[58,59] Both of these drugs have weak enzyme-inducing properties. In one case report, levetiracetam was associated with reduced plasma levels of rivaroxaban.[60] However, the authors'

suggestion that levetiracetam may act as a P-glycoprotein inducer remains controversial.[61]

POTENTIAL LONG-TERM EFFECTS ON VASCULAR RISK

Several studies have associated first-generation ASMs with alterations in serological markers of vascular risk. Carbamazepine, phenytoin, and valproic acid are amongst the most commonly studied drugs and have been linked to elevated LDL and total cholesterol levels.[62-65] Carbamazepine and phenytoin have also been associated with higher HDL levels, while valproic acid, conversely, has been connected to decreased levels, suggesting a worse lipid profile.[65] Furthermore, enzyme-inducing ASMs have been linked to abnormalities of lipoprotein(a), C-reactive protein, and homocysteine, whereas valproic acid has been associated with weight gain, hyperinsulinemia, insulin resistance, and metabolic syndrome.[64,66]

Some studies have investigated the risk of stroke and myocardial infarction stratified by ASM treatment. A Danish nationwide study found that patients with epilepsy receiving carbamazepine had a higher risk of cardiovascular death than those treated with lamotrigine and a higher risk of myocardial infarction and stroke compared with those treated with valproic acid.[13] The use of oxcarbazepine was associated with an even higher hazard of stroke and death, which cannot be explained solely by its weak enzyme-inducing properties. Two other population-based studies have examined if enzyme-inducing agents increase the long-term risk of cardiovascular events but yielded conflicting results.[67,68]

There have been speculations that valproic acid may reduce the risk of cardiovascular disease by inhibiting the gene histone deacetylase 9, which has been associated with large artery disease.[69] While there is some evidence that patients receiving valproic acid have a lower risk of cardiovascular events compared with enzyme-inducing drugs,[69,70] it has also been associated with increased carotid artery intimal-medial thickness (a marker for large artery disease and stroke).[71]

QUANTIFYING THE RISK OF STROKE IN PERSONS WITH LATE-ONSET SEIZURES OR EPILEPSY

Multiple investigators have described that epilepsy can precede stroke.[9,10,72] A case-control study published in 1987 reported that 4.5% of cases with a first-ever stroke had preexisting epilepsy compared to 0.6% of elective surgical controls.[10] That observation was later supported by results from the Oxfordshire community stroke project, in which 3% had seizures or epilepsy preceding stroke.[72] For comparison, the point prevalence of active epilepsy among persons over 60 years of age is about 0.7%.[5,73]

More recent studies have reported a lower proportion of preexisting epilepsy among stroke cases. In Paper I, we used the Swedish Stroke Register (Riksstroke[74]) along with health care administrative data to determine how often seizures precede stroke on a national scale.[75] Among 92 596 subjects over 60 years of age with a first-ever stroke in 2005–2010, 1.48% (n=1372) had a first seizure-related diagnostic code (G40 [epilepsy], G41 [status epilepticus], or R56.8 [seizures]) registered more than three days and less than 10 years before the stroke. Interestingly, a history of seizures was more common among patients with intracerebral hemorrhage (ICH; 1.94%) than acute ischemic stroke (AIS; 1.42%).

At first glance, these relatively modest figures might raise concerns about the classification of seizures or epilepsy. The National Patient Register [NPR[76]] – the source of seizure-related diagnostic codes in this thesis – contains information from all hospitals and outpatient clinics (including emergency rooms), but not the primary care. We will not have captured patients who have been assessed for seizures or epilepsy solely by their general practitioner. This scenario is, however, relatively rare, since new-onset seizures usually result in an emergency room visit or referral to a neurologist. In addition, our findings were recently corroborated by data from a population-based Taiwanese study, which found evidence of preexisting epilepsy in 6913 (1.45%) out of 484 990 stroke patients.[77]

A more likely explanation would be that stroke detection has increased overall. Significant advances in brain imaging have made it possible to diagnose stroke

in persons without traditional clinical stroke syndromes. Conversely, a diagnosis of epilepsy is still almost always based solely on clinical history.

THE ABSOLUTE RISK OF STROKE

To estimate the 10-year risk of stroke after a first seizure, we used regional incidence figures along with population statistics. According to the Stockholm Incidence Registry of Epilepsy study (SIRE[78]), incidence rates of late-onset seizures vary between 19.1 per 100 000 person-years among persons 40-44 years of age and 53.1 per 100 000 person-years in those over 85.

The results of our calculations are displayed in Table 1.[75] The number of individuals with an onset of seizures less than 10 years before stroke was divided by the expected number of new-onset unprovoked seizures in Sweden during 10 years. The proportion reflects the absolute risk of stroke after a first seizure, and indicates that about 10-12% of all new-onset seizures after middle age will herald a subsequent stroke within 10 years. Of note, the denominator includes remote symptomatic seizures after stroke, suggesting the calculated risk estimates may be conservative. The findings are in line with a previous retrospective cohort study, in which 10.0% of persons over the age of 60 with unexplained seizures or epilepsy had a stroke during a median follow-up of 5.3 years.[11] Putting the results into context, the 5-year risk of stroke following a transient ischemic attack is about 9.5%, but that is after risk reduction measures.[79]

Table 1. *Proportions of seizures that could herald a subsequent stroke within 10 years. The expected number of seizures was based on incidence rates for each age group in the Stockholm Incidence Registry of Epilepsy study and Swedish population statistics from 2007. The range reflects the 95% confidence intervals of incidence rates.*

Age at sz onset	N pre-stroke sz	Expected N of sz	Proportion
50-59	174	3000-3307	5.3%-5.8%
60-69	400	4330-4438	9.0%-9.2%
70-79	494	2572-3672	13%-19%
80-89	281	1378-2199	13%-20%
90-100	23	251-401	5.7%-9.1%
All	1372	11531-14017	9.8%-11.9%

Table 2. *Studies providing data on the relative risk of subsequent stroke in patients with seizures or epilepsy. R = retrospective*

Author	Country	Design	Study period	Population	Control group	Adjusted HR/OR (95%CI)
Cleary 2004	UK	R, cohort	Not reported	4 709 individuals with onset of unexplained seizures after the age of 60.	Randomly selected 1:1, matched for age, sex and general practice.	**2.89** (2.45–3.41)
Chang 2014	Taiwan	R, cohort	2000-2009	3 812 individuals with onset of epilepsy and ASM treatment after the age of 20.	Randomly selected 1:4, matched for age, sex and vascular comorbidities.	**2.92** (2.58–3.30)
Wannamaker 2015	USA	R, cohort	2002-2011	21 035 individuals with onset of unexplained epilepsy after the age of 35.	16 638 controls hospitalized or having visited the emergency department with an isolated lower extremity fracture.	**1.60** (1.42–1.80)
Hsu 2019	Taiwan	R, cohort	2000-2013	6 746 individuals with onset of epilepsy after the age of 20.	Randomly selected 1:4, matched for age and sex.	**2.24** (2.02–2.49)
Larsson 2020	Sweden	Case-control	2001-2009	123 105 cases ≤100 years of age with a first-ever stroke.	Randomly selected 1:2, matched for age and sex.	**1.68** (1.56–1.80)

THE RELATIVE RISK OF STROKE

Five studies, including Paper II, have reported relative risk estimates of stroke (all stroke types) following the onset of unprovoked seizures or epilepsy.[11,77,80-82] Table 2 displays the details of these studies. Another Danish register-based study has provided HRs of ischemic stroke exclusively.[13] All studies were population-based, and all but one used nationwide data sources. The study populations were heterogeneous in regard to age structure, but they all comprised persons with unprovoked seizures or epilepsy without a history of cerebrovascular disease.

Paper II used case-control methodology to estimate the risk of stroke, stratified by stroke type, age, sex, and time between seizure onset and stroke (or index date for controls).[82] All cases ≤100 years of age with a registered acute stroke event 2001-2009 were identified in the Swedish Stroke Register. Two controls per case, matched for sex and age at the year of stroke onset, were randomly drawn from the Swedish population. The selection of controls was thus not based on health care administrative data, which only encompasses individuals with health care encounters. Lastly, a history of prior cerebrovascular disease, traumatic head injury, or brain tumor resulted in exclusion, leaving 123 105 first-ever stroke cases and 250 506 stroke-free controls.

The overall OR of stroke was 1.77 (95%CI 1.65–1.89), which decreased to 1.68 (95%CI 1.56–1.80) after adjustments for hypertension, diabetes mellitus, and atrial fibrillation.[82] Previously reported HRs have ranged between 1.60 and 2.89.[11,77,80,81] Similarly to the two studies from Taiwan[77,80], we found that the relative risk decreased with age, suggesting that persons with epilepsy more often develop their first stroke in younger ages (50–74 years, OR 2.16 [95 % CI 1.96–2.39]; ≥75 years, OR 1.40 [95 % CI 1.27–1.55]).[82]

Table 3 displays previously reported relative risk estimates for stroke subtypes.[13,77,80,82] The increased risk of intracerebral hemorrhage (ICH) may reflect undetected hypertension, underlying leukoaraiosis, or cerebral amyloid angiopathy.[83,84] Previous studies have demonstrated higher hazard ratios for ICH than acute ischemic stroke (AIS), but ours is the first study to show a statistically significant difference. However, the reader should interpret this finding with caution since we did not have access to data on potential confounders, such as treatment with anticoagulants. Unfortunately, the

Swedish Stroke Register does not include information about stroke location (e.g., lobar vs. non-lobar ICH).

Table 3. *Studies providing data on the relative risk of specific stroke subtypes.*

	Stroke type, HR/OR (95%CI)	
Author	**AIS**	**ICH**
Olesen 2011[13]	**2.22** (2.09–2.36)	-
Chang 2014[80]	**2.85** (2.49–3.26)	**3.30** (2.46–4.43)
Hsu 2019[77]	**1.91** (1.62–2.26)	**2.27** (1.80–2.85)
Larsson 2020[82]	**1.57** (1.45–1.70)	**2.57** (2.10–3.14)

In Paper II, we also stratified ORs by time between the onset of seizures and subsequent stroke. In subjects with a first seizure in the year before stroke, the OR was significantly higher (2.21, 95%CI 1.79-2.72) than in those with a first seizure five years or more before stroke (1.57, 95%CI 1.43–1.72). The finding suggests that the risk of stroke is highest soon after seizure diagnosis, which indicate that any evaluation of cardiovascular risk factors should be performed early on. Previously, an English study have described that stroke followed shortly after seizure onset in three cases.[10]

IMPLICATIONS FOR MANAGEMENT

A growing body of evidence suggests persons with epilepsy are at an increased risk of cardiovascular morbidity. The results from Papers I-II indicate that a significant proportion of all new-onset seizures after middle age will herald a subsequent stroke. Using incidence data and population statistics, we estimated the 10-year risk of stroke to be about 10-12%, with estimates varying between 5-20% depending on age group. In relative terms, the risk appears to be almost two-fold compared to age-matched controls from the general population – and higher during the first year after seizure onset.

It is not possible to draw any conclusions from the findings of Papers I-II on the causal effects of seizures or epilepsy on stroke risk. Multiple confounders are present, including vascular risk factors, covert cerebrovascular disease, and the use of ASMs, which may alter vascular risk. Regardless of the cause, seizures after middle age constitute a marker for increased vascular risk. This could provide opportunities, as it is possible that a tailored management approach (which remains to be defined) to minimize stroke risk in persons with late-onset seizures has the potential to improve health outcomes.

Whether persons with an onset of unprovoked seizures late in life should undergo vascular risk assessment is a debated issue. Advocates of screening emphasize that, in theory, lifestyle changes and pharmacological management of risk factors should reduce stroke risk.[12,85] As of yet, there is no high-level evidence of preventive interventions to support this claim.

Assuming late-onset seizures reflect underlying cerebrovascular disease, can experiences from other study populations provide further guidance? Disappointingly, there is also a lack of evidence regarding preventive interventions in patients with silent brain infarcts and white matter hyperintensities.[44] The highest degree of evidence (or least low) is for blood pressure management, which seems to slow down the progression of severe small vessel disease.[86] Nevertheless, because covert cerebrovascular lesions are associated with an increased risk of vascular events and death, the American Heart Association and the European Stroke Organization recommend management according to existing primary prevention guidelines.[44,86] Of note, the risk of future stroke in patients with silent brain infarcts (HR_{adj} 1.5-3.3[42,43,87,88]) seems to be of a similar magnitude to that reported in patients with late-onset seizures.

It certainly seems that intervention is warranted, but how, when, and to whom remains unclear. A possible first step would be to elucidate if previously undetected vascular risk factors, including physical inactivity and smoking, are common among patients with new-onset seizures after middle age. Those with undiagnosed hypertension would arguably benefit the most from cardiovascular intervention. Then, randomized evidence is likely needed to inform clinical practice. The study design might include one group randomized to cardiovascular evaluation and another receiving standard care. If such a study demonstrated that vascular risk assessment is beneficial, it would change clinical practice worldwide.

Regarding treatment of epilepsy, the clinician should be aware that late-onset seizures predict an increased risk of subsequent stroke, thus avoiding enzyme-inducing ASMs when fully appropriate alternatives are available.

5 SEIZURES AND EPILEPSY AFTER STROKE

Globally one in four adults will have a stroke in their lifetime.[89] A substantial proportion of these patients will develop seizures, which are divided into early and late poststroke seizures depending on the temporal relation with the preceding stroke. Early seizures occur within one week after stroke, usually in the first two days, and are generally deemed to be acute symptomatic.[90] A single late poststroke seizure, on the other hand, is associated with a high recurrence risk (at least 60%[91]) and therefore considered poststroke epilepsy.[2]

Poststroke epilepsy management decisions must incorporate age, comorbidity, potential drug interactions, and stroke survivors' general vulnerability. As discussed in the previous chapter, persons with unexplained late-onset seizures have increased vascular risk. Persons with poststroke epilepsy constitute a highly selected population with even more pronounced vascular risk, high mortality, and specific drug-drug interactions related to secondary stroke prophylaxis.

The evidence to guide management in patients with poststroke epilepsy is sparse, but there have been some advances in recent years. These include a progressive increase in the use of newer ASMs and increased awareness that patients are suboptimally managed. This chapter gives a brief overview of the literature, presents Papers III-IV, and discusses the management of persons with poststroke epilepsy, focusing on prognostic aspects of ASM use.

! The sub-chapter **Treatment of persons with poststroke epilepsy** presents Papers III-IV

EPIDEMIOLOGY

The long-term cumulative incidence of poststroke epilepsy varies greatly (2-15%) depending on study population, methodology, and the duration of follow-up.[29,72,92-104] Seizures are generally about twice as common after ICH than AIS.[105] A Swedish nationwide study (n=106,455), based on the same data set as Papers I, III, and IV of this thesis, has identified poststroke epilepsy in 7.3% of two-month stroke survivors (AIS 6.7%; ICH 12.4%; mean follow-up 4.8 years).[106] This aligns well with results from other studies using primary sources like medical records or interviews with long-term follow-up after stroke. The largest (n=3,310) prospective population-based study to date, based on the South London Stroke Register, reported a risk of 6.4% after a mean follow-up of 3.8 years (AIS 6.1%; ICH 8.1%).[100] More recently, a sizable Finnish retrospective study of three-month ICH survivors reported a cumulative incidence of 13.5% based on medical records (median follow-up 6.4 years).[107]

PREDICTION AND PATHOPHYSIOLOGY

Only a subgroup of all stroke patients develops epilepsy. Factors behind the epileptic susceptibility in a given individual remain unknown, but there are clues on a group level. The nature and extent of the damage are paramount. Severe strokes, cerebral hemorrhage, cortical involvement, and anterior circulation infarcts increase the risk of poststroke epilepsy.[94,100,101,105] Young age at stroke onset has been associated with an increased risk in some studies,[100,104] but there have been suggestions that this finding might be due to survivorship bias.[108] Early poststroke seizures are generally considered to reflect temporary local metabolic disturbances rather than a long-term predisposition to generate seizures, but are nonetheless associated with subsequent poststroke epilepsy.[90,91]

Several clinical prediction tools exist that use different combinations of the above factors to determine the risk of poststroke epilepsy.[109-111] The SeLECT score combines five items to predict the risk of epilepsy following an ischemic stroke; scores for each item produce an overall result ranging between zero and nine.[111] A score of zero indicates a low 5-year risk of poststroke epilepsy (1.3%, 95%CI 0.7-1.8), whereas a score of nine suggests an 83% risk (95%CI 62-93). The CAVE score incorporates four parameters to predict the risk of epilepsy after an ICH, ranging from 0.6% in patients with zero points to 46% in patients with the highest score, four points.[110]

Typically, there is a latency between stroke and the onset of epileptic seizures. The median time is about one year, and over 80 percent of patients who develop epilepsy do so within two years.[29,106] During this time, it is thought that the brain undergoes a process called epileptogenesis, which gives rise to an epileptic predisposition. Little is known about this process, which may comprise a wide array of pathological mechanisms.[112] Animal models could eventually allow for preventive treatment trials, but so far, modeling has proven difficult, and very few of the studied cellular changes have been linked to epileptogenesis.[113,114] In humans, there is evidence that blood-brain barrier dysfunction may make the brain more susceptible to seizures.[115] A correlation between late poststroke seizures and blood-brain barrier disruption has been reported.[116]

PRIMARY PREVENTION OF POSTSTROKE EPILEPSY

The latent period in which epileptogenesis occurs could provide an opportunity to avert or modify epilepsy, but so far, no efforts have proven successful.[108,117,118] Many commonly used drugs, including atorvastatin, losartan, levetiracetam, brivaracetam, gabapentin, and eslicarbazepine acetate, seem to have antiepileptogenic effects in animal models.[119] Nevertheless, very few translational clinical trials have been conducted.

Two RCTs have investigated the use of ASMs for primary prevention of seizures after stroke.[120,121] One aimed to compare treatment with levetiracetam against placebo but failed to recruit enough participants.[120] Another study randomized 72 patients with ICH to short-term (4 weeks) treatment with either valproic acid or placebo; the treatment group had a non-significant reduction of early seizures, but the occurrence of epilepsy did not differ after one year.[121] In addition, there is an ongoing double-blind RCT comparing short-term (12 weeks) treatment with perampanel against placebo.[122]

Observational evidence have suggested that some drugs used in secondary stroke prevention may modify seizure occurrence. The most interesting finding surrounds statin use, which has been associated with a reduced risk of early seizures after stroke (OR 0.35, 95%CI 0.20–0.60).[29] Moreover, those with early seizures had a reduced risk of poststroke epilepsy. Other drugs that may reduce the risk of seizures include furosemide and thiazides.[123]

PROGNOSIS IN POSTSTROKE EPILEPSY

The sections below address different aspects of prognosis in poststroke epilepsy, including survival, seizure freedom rates, and influence on stroke rehabilitation. The impact of specific ASMs on prognosis will be discussed in the next section.

SEIZURE FREEDOM

In general, two-thirds of persons with epilepsy achieve seizure freedom with ASM treatment.[124,125] Early treatment response is an important predictor of the long-term prognosis. Of those who eventually achieve seizure freedom, 90% attain control with their first or second ASM.[125]

Poststroke epilepsy is generally considered easy to treat, and several reviews conclude that monotherapy usually suffices to achieve seizure control.[105,126] Prospective clinical trials have reported seizure freedom rates (varying definitions) of 70–90% with monotherapy.[127-131]

If seizure control in poststroke epilepsy is, in fact, easily attainable, there may be opportunities to improve management. Real-world data from small observational studies have reported varying, but generally somewhat lower, remission rates.[132-136] In some study populations, less than 60% achieve seizure control.[132,134] A Swedish observational study reviewed the medical records of 24 patients with continuous seizures and surprisingly found that in half of them, no treatment revision had been made at all.[136] A shortage of neurologists may play a role, since most patients had follow-up visits with physicians specialized in other areas (e.g., internists, or general practitioners).

REHABILITATION

Most stroke patients recover some abilities over time. The greatest gains in recovery occur early after stroke, and clinically significant improvements are typically only seen within the first few months.[137,138] Poststroke epilepsy usually occurs later on, but early seizures could, in theory, have harmful effects on the recently damaged brain, interfere with stroke rehabilitation or lead to ASM treatment which, in turn, may have adverse effects.

Only a few studies have investigated the impact of seizures on long-term disability. A Dutch study has reported an independent relationship between

poststroke epilepsy and poorer long-term outcome (modified Rankin Scale [mRS] >2) in young adults with ischemic stroke.[139] The finding is supported by a study of 257 stroke patients receiving IV thrombolysis, in which seizures were associated with a three-fold risk of unfavorable outcome (mRS 2-6 [including death]).[140] However, this finding may not apply to older age groups, as other studies have failed to demonstrate any relevant differences in multivariable models.[93,141,142] Nevertheless, experts believe that seizures can contribute to morbidity after stroke, at least in those difficult to treat.[143,144] Frequent seizures, along with depression and severe stroke sequelae, are independent predictors of decreased health-related quality of life among persons with poststroke epilepsy.[145]

SURVIVAL

Poststroke epilepsy combines the two leading neurological causes for premature mortality worldwide.[146] Studies on long-term mortality have so far yielded conflicting results.[91,140,147-149] A methodological issue concerns the latency between stroke and epilepsy, which could lead to survivorship bias if those who survive long enough to develop poststroke epilepsy are compared to patients at risk of short-term mortality after stroke. In the largest cohort study to date, patients with poststroke epilepsy (mean age 75 years) had an increased risk of death (HR 1.69, 95%CI 1.64–1.74) compared to two-month stroke survivors, also after adjustments for stroke severity.[149] In light of the high baseline mortality after stroke, a more than 60% risk increase must be considered substantial.

The reason for the increased mortality remains unknown. People with epilepsy face excess mortality due to sudden unexpected death in epilepsy and seizure-related accidents. Those at the highest risk have uncontrolled epilepsy and a high frequency of generalized seizures.[150] As poststroke epilepsy is considered to respond well to treatment, this should not influence survival to any great extent. Instead, an increased risk of cardiovascular events is suspected of contributing to the finding. The cause of death in epilepsy is often linked to the underlying etiology of epilepsy, and more so if death occurs within the first few years of the epilepsy diagnosis.[151] Our research group has previously studied the data set used in Paper III-IV to investigate causes of death in both poststroke epilepsy and the general stroke population, and most deaths are caused by vascular disease.[152] Only 0.9% of the patients with poststroke

epilepsy had epilepsy or status epilepticus registered as an underlying cause of death.

TREATMENT OF PERSONS WITH POSTSTROKE EPILEPSY

Most persons with epilepsy are treated with ASMs to reduce the risk of seizure recurrence. The decision to start treatment depends on seizure type, frequency, risk of adverse effects, and the individual patient's preference. There might be reasons to refrain from treatment in some cases, such as when there is a high risk of adverse effects in combination with 'mild' focal seizures.

The treatment of older adults poses a particular challenge. Age-related physiological changes alter the pharmacokinetics of many ASMs, which means doses can often be reduced while still achieving adequate serum concentrations. It also affects pharmacodynamic sensitivity, leading to increased susceptibility to adverse effects.[153] Moreover, the risk of drug interactions is significant, as comorbidities and related therapies are common.

This section reviews the evidence for the use of specific ASMs in persons with poststroke epilepsy. Additionally, Papers III-IV are presented and discussed.

THE PRESCRIBING PATTERN FOR POSTSTROKE EPILEPSY

In Papers III-IV, we used the Swedish Stroke Register (Riksstroke[74]) along with health care administrative data (the NPR[76]) to identify a nationwide cohort of adults with poststroke epilepsy. Individual-level data on dispensed ASMs (substances and dispensation dates) were collected from the Swedish Prescribed Drug Register (SPDR[154]) and linked to the data set. Figure 2 illustrates the eligibility process. A total of 4991 individuals had a first-ever ASM dispensation following poststroke epilepsy.[155]

Previously, a study based on the Taiwan National Health Insurance Research Database has used a similar methodology to identify patients with poststroke epilepsy.[156] They reported that 2.5% of all stroke patients developed poststroke epilepsy and received an ASM prescription, which is lower than the proportion in the above data set (3.9%). Combining a diagnostic code and an ASM prescription usually results in a high positive predictive value for epilepsy,[157] indicating that the discrepancy may primarily be due to differences in sensitivity.

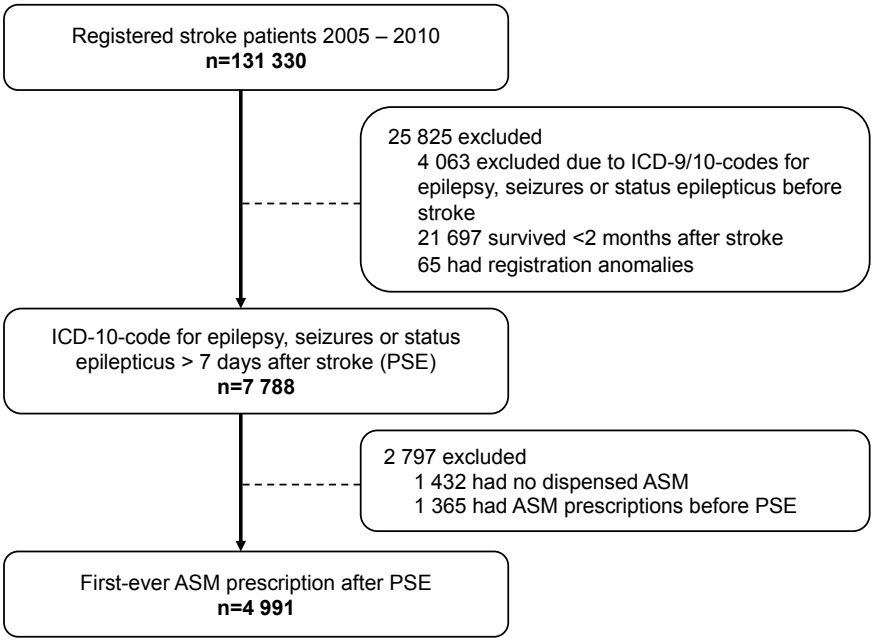


Figure 2. *Flow chart of the eligibility process of Paper III.*

During the study period (2005-2014), carbamazepine was the most frequently prescribed first ASM (n=2373), followed by valproic acid (n=943), and levetiracetam (n=555).[155] Internationally, first generation ASMs are commonly used among older adults with new-onset epilepsy.[156,158-160] Sweden is no exception.

Figure 3 illustrates the prescribing pattern of first ASMs between 2005 and 2014.[155] There is a clear trend for second-generation ASMs, particularly levetiracetam. The shift may be due to an increased awareness of the safety advantages over older generation agents, or that levetiracetam is easy to titrate. However, first-generation ASMs, and carbamazepine, in particular, were still commonly employed at the end of the study period.

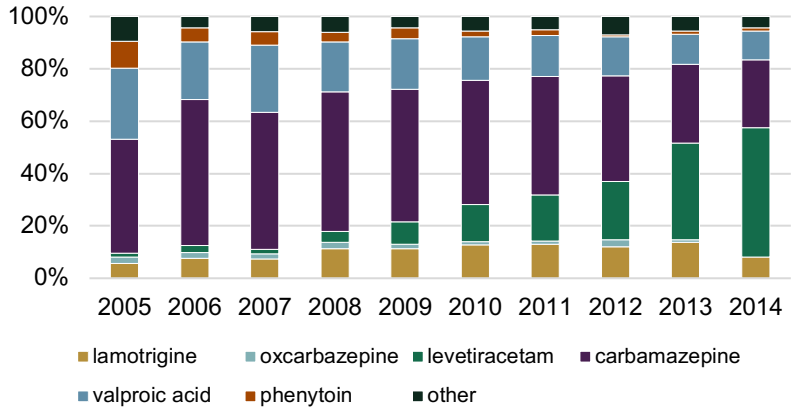


Figure 3. *Proportions of first ASM prescriptions during the study period.*

Some of the baseline characteristics differed between patients receiving different ASMs, which merit some consideration.[155] Atrial fibrillation and statin use were relatively less prevalent among patients receiving enzyme-inducing drugs (carbamazepine, phenytoin), possibly suggesting some awareness of interactions with anticoagulants and statins. However, the prevalence of statins increased significantly in all ASM groups during the study period (data not shown), reflecting general improvements in stroke care. In 2012, 70% of the patients with carbamazepine had statin prescriptions compared to 80% of patients with levetiracetam (data not published).

Persons prescribed valproic acid were generally older and lived at assisted living facilities or nursing homes more often, especially compared to those treated with levetiracetam. This may, to some degree, reflect differences in access to epilepsy services. There is evidence that second-generation ASMs to a greater extent are prescribed by neurologists rather than by other specialists and that being old means being less often treated by a neurologist.[161]

RANDOMIZED EVIDENCE FOR ASM SELECTION

Two randomized open-label trials have been comparing different ASMs in poststroke epilepsy.[127,162] An Israeli study randomized 64 patients with a first poststroke seizure to treatment with either lamotrigine or carbamazepine.[127] After up to 12 months of follow-up, 72% of those receiving lamotrigine, and 44% in the carbamazepine arm, were without recurrent seizures (non-significant difference; p = 0.06). A higher number of patients in the carbamazepine arm withdrew from the study due to adverse events (31% vs. 3%, p = 0.02). The second study compared levetiracetam against carbamazepine but found no significant difference in seizure freedom after one year (94% vs. 85%; p=0.08).[162] The number of participants who discontinued the trial prematurely did not differ between the groups, but adverse effects were more common among those treated with carbamazepine (57% vs. 46%; p = 0.02).

The above studies were not of sufficient sample size to evaluate differences in seizure freedom rates. Still, the results align with RCTs in older adults with focal epilepsy of mixed etiologies, which have shown that second-generation ASMs (gabapentin[163], lacosamide[164], lamotrigine[163,165-167], levetiracetam[168]) are better tolerated than carbamazepine. Interestingly, a recent meta-analysis of the two studies reported that the occurrence of adverse effects might be higher for levetiracetam than lamotrigine (OR 6.87, 95%CI 1.15-41.1).[169]

NON-RANDOMIZED EVIDENCE FOR ASM SELECTION

Prospective, uncontrolled trials have studied the efficacy and tolerability of gabapentin, levetiracetam, and eslicarbazepine acetate in poststroke epilepsy. Among 71 patients treated with gabapentin, 18% experienced recurrent seizures, and 6% discontinued treatment, during a mean follow-up of 30 months.[128] Two small studies have assessed levetiracetam; they reported comparable seizure freedom rates (82% vs. 77%) but somewhat diverging retention rates (91% vs. 80%) after a mean follow-up of 18 months.[129,130] In 76 patients treated with eslicarbazepine acetate, the 12-month retention rate was 88% (higher than among non-poststroke epilepsy patients [77%]).[170]

Some studies, including Papers III-IV, have used real-world data to make direct comparisons between ASMs. A Taiwanese large population-based cohort study ‘assessed the efficacy’ by comparing emergency room visits and hospitalizations due to seizures between various ASMs.[171] They concluded that

patients treated with valproic acid, carbamazepine, or 'new ASMs' had better seizure control than the reference group treated with phenytoin. While the study has some important limitations, it was the first large-scale observational cohort study to assess different ASMs in poststroke epilepsy.

The study described in Paper III used time-to-event analysis to investigate the long-term retention rates of six common ASMs in the nationwide cohort described above (n=4991).[155] The SPDR provided individual-level data on all dispensed ASMs, which formed the basis for a treatment algorithm (Figure 4). We considered the treatment ongoing as long as the individual had at least two dispensations of the same ASM per rolling 12 months. When the prescription had not been filled for a year, treatment discontinuation occurred (event). The retention rates are provided in Table 4 and illustrated in Figure 5.[155]

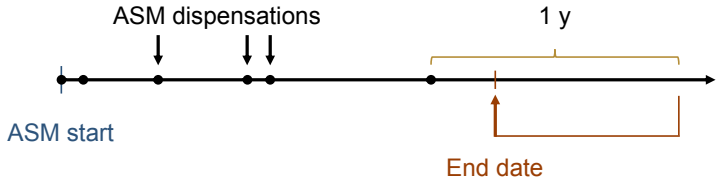
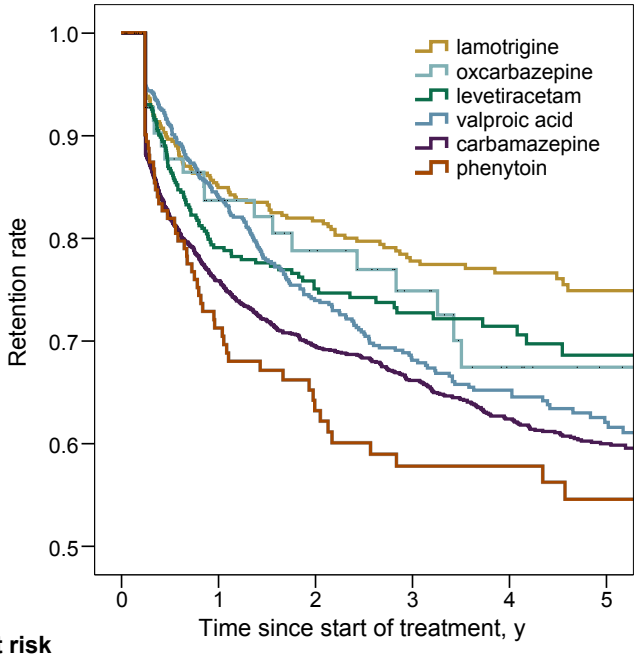


Figure 4. *Illustration of the treatment algorithm used in Papers III-IV. The treatment was considered ongoing as long as the same ASM substance was dispensed regularly (≥2 times per rolling 12 months). If treatment discontinuation occurred, the length of treatment time was calculated until 90 days after the last drug dispensation.*

Table 4. *Retention rates for six selected ASM in poststroke epilepsy.*

	1-year		3-year		5-year	
ASM	%	95%CI	%	95%CI	%	95%CI
lamotrigine	85	82-88	78	74-82	75	70-79
levetiracetam	79	75-83	73	68-77	69	63-74
oxcarbazepine	84	76-92	75	65-85	68	55-80
valproic acid	84	81-86	68	64-72	62	58-66
carbamazepine	76	74-78	66	64-68	60	58-62
phenytoin	71	64-79	58	49-67	55	45-64



At risk						
lamotrigine	519	363	298	234	166	107
oxcarbazepine	89	57	45	34	23	18
levetiracetam	554	284	191	136	88	39
valproic acid	943	561	386	277	199	129
carbamazepine	2371	1409	1083	861	646	446
phenytoin	174	88	63	47	39	29

Figure 5. *Kaplan-Meier curves illustrating retention rates for six selected ASMs in poststroke epilepsy.*

We found higher 3-year and 5-year retention rates for lamotrigine compared with all first-generation ASMs. At five years, both lamotrigine and levetiracetam had a significantly higher retention rate than carbamazepine. The exact values should be interpreted with caution, as the definition of treatment discontinuation is conservative and the rates therefore might have been overestimated. Those who die within a year from their last ASM dispensation will not get an event, even if treatment was discontinued.

Some data can be extracted from the slopes of the Kaplan-Meier curves in Figure 5. When an event (discontinuation) was triggered, the last day of treatment occurred 90 days after the last drug dispensation, explaining why no patient discontinued treatment in the first three months. The steep decline

thereafter reflects patients who stopped treatment after a single or a few dispensations. Early discontinuation more often occurred in patients treated with carbamazepine and phenytoin. This might reflect a higher rate of adverse effects early on or the use of phenytoin in the acute treatment of status epilepticus. Conversely, valproic acid had a relatively high retention rate at the beginning and a substantial decline in the later years, possibly suggesting more long-term adverse effects.

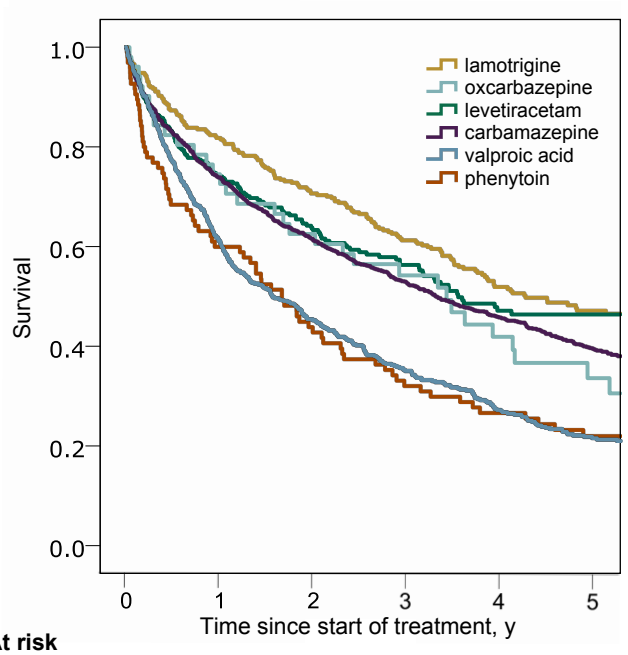
Finally, we used Cox regression models to estimate the relative hazard of discontinuation. Patients prescribed lamotrigine or levetiracetam had a lower risk of treatment discontinuation compared with carbamazepine, also in the multivariable model (Table 5). The findings align with the results from RCTs in older adults (various etiologies), which have reported that the relative risk of discontinuation is about twice as high in patients receiving carbamazepine, mainly due to worse tolerability.[165,167,168]

Paper IV used the same data set and a similar methodology but investigated if mortality varied with different ASMs.[172] Of those with poststroke epilepsy and a first-ever ASM dispensation, 2577 patients with persistent ASM monotherapy (no switch or add-on) were included in the study. The primary outcome was all-cause death, but we also studied death from cardiovascular disease as a secondary outcome. In the latter case, other causes of death were considered competing risks.

Table 5. *Crude and adjusted hazard ratios of initial ASM treatment discontinuation, assessed with Cox regression.*

	Crude (n=4986)		Adjusted[a] (n =4114)	
	HR	95%CI	HR	95%CI
carbamazepine	ref		ref	
valproic acid	0.82	0.71-0.95	0.88	0.75-1.03
levetiracetam	0.77	0.64-0.94	0.75	0.60-0.94
lamotrigine	0.56	0.45-0.69	0.53	0.43-0.67
phenytoin	1.18	0.90-1.54	1.14	0.84-1.54
oxcarbazepine	0.74	0.48-1.13	0.90	0.57-1.40

[a]Adjustments for age, sex, stroke type, living arrangements before and after stroke, mobility before and after stroke, hypertension, atrial fibrillation, diabetes mellitus, statin use, and year of treatment start.



At risk						
lamotrigine	349	278	230	184	125	83
levetiracetam	376	214	148	105	65	28
oxcarbazepine	51	38	31	24	16	11
carbamazepine	1357	977	789	630	486	336
valproic acid	569	338	245	175	121	80
phenytoin	95	56	40	30	24	18

Figure 6. *Kaplan-Meier curves illustrating survival for individuals with one of six studied ASMs in poststroke epilepsy.*

There were 1550 deaths overall, with 63% considered due to a cardiovascular cause. Figure 6 displays the survival function for all-cause death stratified for selected ASMs. The differences in 3-year and 5-year survival between lamotrigine, carbamazepine, and valproic acid were statistically significant.

Table 6 provides adjusted hazard ratios of all-cause and cardiovascular death.[172] Our findings suggest survival varies in patients treated with different ASMs, also after various adjustments, including markers for stroke severity. Patients receiving lamotrigine had significantly lower mortality than the reference group treated with carbamazepine. The group with valproic acid had an increased risk of death, while patients treated with levetiracetam had a reduced risk of cardiovascular death.

Table 6. *Adjusted hazard ratios of all-cause and cardiovascular death in 2577 patients with poststroke epilepsy and ASM monotherapy, stratified for six selected ASMs. All-cause death was assessed with Cox regression, while cardiovascular death was assessed with Fine and Gray competing risk regression.*

	All-cause death		Cardiovascular death	
	HR[a]	95%CI	HR[a]	95%CI
carbamazepine	ref		ref	
lamotrigine	0.72	0.60-0.86	0.76	0.61-0.95
levetiracetam	0.96	0.80-1.15	0.77	0.60-0.99
valproic acid	1.40	1.23-1.59	1.40	1.19-1.64
phenytoin	1.16	0.88-1.51	1.02	0.71-1.47
oxcarbazepine	1.16	0.81-1.66	0.71	0.42-1.18

[a]Adjustments for age, sex, stroke type, living arrangements before and after stroke, dependency in activities of daily living before and after stroke, status epilepticus, hypertension, atrial fibrillation, diabetes mellitus, statin use, antidepressant use, and smoking. Missing covariate data has been imputed.

As discussed in chapter 4, concerns have been raised that first-generation ASMs, particularly the strong liver enzyme inducers, may increase vascular risk. The difference in mortality between lamotrigine and the older agents reinforces those concerns, although it is not possible to ascertain causality.[172] The results are less likely to be explained by epilepsy severity or changes in the prescription pattern over time. The study population only included subjects on persistent monotherapy, suggesting a selection of those easy to treat. Furthermore, patients treated with carbamazepine had less frequent hospital admissions due to seizures during follow-up (compared to lamotrigine and valproic acid, respectively), and epilepsy or seizures were also less commonly listed as a contributing cause of death in the carbamazepine group. Sensitivity analyses adjusted for the year of treatment start did not impact HRs.

However, the markedly increased mortality in persons treated with valproic acid was unanticipated, as some studies have linked valproic acid to reduced risk of myocardial infarction and stroke compared with carbamazepine.[13] The finding may suggest persons with poststroke epilepsy are particularly susceptible to valproic acid's influence on cholesterol levels and disturbances associated with the metabolic syndrome. Other possible explanations include confounding or central nervous system adverse effects (e.g., valproate encephalopathy).[173] Further studies are needed to verify this finding, but until then, caution is warranted.

IMPLICATIONS FOR MANAGEMENT

The lack of high-quality, randomized studies indicates that there might be challenges in including or following patients with poststroke epilepsy. Under such circumstances, we can rely on evidence from other (usually healthier) study populations or turn to observational studies. Both approaches complement one another.

Papers III-IV used register-based methodology to investigate prognostic aspects of ASM treatment. In Paper III, the risk of treatment discontinuation was lower for lamotrigine and levetiracetam compared with carbamazepine. While it is impossible to know why the subjects in our cohort discontinued their treatment, the findings from small RCTs suggest differences in tolerability to be the main explanation.[127,162] Overall, lamotrigine and levetiracetam seem well tolerated by persons with poststroke epilepsy, aligning with results from RCTs in older adults with epilepsy of various etiologies.[165,167,168]

Paper IV reported another reason to think twice about prescribing carbamazepine as first-line treatment in poststroke epilepsy; patients receiving lamotrigine or levetiracetam had significantly lower cardiovascular mortality. The findings fuel concerns over ASMs' effects on cardiovascular risk markers and interactions with drugs used in secondary stroke prevention. Avoiding enzyme-inducing agents and valproic acid seems reasonable when fully appropriate alternatives are available. The finding is also interesting considering the US Food and Drug Administration's recent addition to the lamotrigine label, which cautions about potential proarrhythmic effects.[174] This might be an issue in some individuals, but lamotrigine does not seem to pose a particular risk on a group level.

Conversely, at the end of the study period (2014), first-generation ASMs were still commonly employed as first-line drugs in poststroke epilepsy. That, and reports of patients not receiving therapy revisions despite continued seizures,[136] suggest that management of the patient group can be improved. Specific and easy-to-follow treatment guidelines for poststroke epilepsy would probably impact the prescription pattern, especially considering that the treating physician often specializes in areas other than neurology. In my opinion, lamotrigine and levetiracetam should be regarded as valid first-line options, while carbamazepine and valproic acid primarily should be reserved for difficult-to-treat cases.

The above findings generate important questions for further research. More evidence is needed regarding ASM efficacy, drug-drug interactions, and the impact of poststroke seizures and ASMs on rehabilitation. Moreover, extensive, prospective studies with long-term follow-up, based on either medical charts or registers, are needed to elucidate the mechanisms behind the increased mortality in patients with poststroke epilepsy.

6 METHODOLOGICAL CONSIDERATIONS

Sweden has a long tradition of maintaining reliable population-based registers with personal data. Numerous registers are available at various Swedish national government authorities, and many of them have complete or nearly complete coverage. Each person with a Swedish citizenship or residence permit (approximately 10.5 million inhabitants) has a unique personal identity number, allowing researchers to link data from different registers to a specific individual.

In addition to the government-administered registers, which usually lack detail, there are more than one hundred Swedish Healthcare Quality Registers that provide disease-specific information. These registers have usually been founded by health care professionals with the purpose to "systematically and continuously develop and safeguard the quality of care."[175]

THE SWEDISH HEALTH CARE SYSTEM

Health care in Sweden is universal for all citizens and largely tax-funded; thus, patient fees for doctor's appointments, emergency room visits, and prescription drugs cover only a small percentage of costs. There are both public and private caregivers. The latter generally provide healthcare under contract with the county councils, which means the same regulations and fees apply. Reporting to the government-administered registers is mandatory for all caregivers.

The Swedish Medical Products Agency and the Regional Drug and Therapeutics Committees provide regularly updated treatment guidelines for common diseases. Generic substitution is mandatory for most reimbursed drugs (however, not for ASMs) unless the treating physician has indicated that no substitutions should be made. To purchase ASMs, the individual needs a valid prescription issued less than a year ago. Most long-term medications are dispensed in 3-month intervals (100-day refills), and every dispensation is automatically reported to the Swedish eHealth Agency.

DATA SOURCES

Papers I-IV are based on five Swedish national registers (Figure 7). A brief description of each register is provided below.

Figure 7. *Overview of the registers used in Papers I-IV.*

THE POPULATION REGISTER

The Population Register covers all residents of Sweden and includes information such as name, sex, date of birth, and address. Once registered, each individual receives a unique personal identification number.

THE SWEDISH STROKE REGISTER

The Swedish Stroke Register, Riksstroke, is the National Healthcare Quality Register for stroke care.[74] It covers information on the entire chain of stroke care, e.g., acute management, comorbidities, stroke prevention, and rehabilitation. All hospitals that admit acute stroke patients participate in the register (>90% coverage in 2012).[176] Three months after the stroke, the patient is asked to participate in a questionnaire follow-up (by letter, phone, or at a return visit), which comprises questions on support and activities of daily living (ADL).[74] If the patient cannot respond, the next of kin or health care personnel may fill in the form (response rate 88%).[176]

NATIONAL PATIENT REGISTER (NPR)

The NPR contains administrative data, including diagnostic coding and admission dates, registered at inpatient care since 1987 and specialized outpatient care since 2001.[76] Coding is based on the ICD-9th/10th revision. In 2017, a primary diagnosis was missing for about 3% of all reported outpatient visits.[177] The positive predictive values of evaluated diagnoses are generally high (for example, multiple sclerosis [93%[178]] and first stroke [94%[179]]). Epilepsy has not been formally validated, but among deceased patients with a prior diagnostic code for epilepsy (G40) in the NPR, 90% fulfill the epilepsy criteria when medical charts are reviewed.[180] Primary care encounters are not recorded in the register, which means the sensitivity for chronic conditions primarily managed by general practitioners is low (for example, dementia [47%[181]]).

THE SWEDISH PRESCRIBED DRUG REGISTER (SPDR)

The SPDR includes information on all drugs issued on prescription by pharmacies in Sweden.[154] Drugs are categorized according to their Anatomical Therapeutic Chemical (ATC) codes. In July 2005, the register was expanded to include patient identities, allowing data linkage with other databases. Prescription data is automatically reported to the Swedish eHealth Agency, which checks the quality of data before recording it in the register.

THE SWEDISH CAUSE OF DEATH REGISTER (CDR)

The CDR contains mortality data for all Swedish residents, regardless of whether the death occurred in Sweden or abroad. The information in the register has been extracted from medical death certificates completed by physicians. In 2015, 0.9% of all deaths were missing an underlying cause.[182]

STRENGTHS AND LIMITATIONS

All epidemiological studies based on nationwide registers essentially share similar limitations and strengths. Data have been collected without any specific research question in mind, meaning the information of interest might be missing or inaccurate. The researcher has no control over the data quality and usually has to rely on previous validations (if available) to assess the risk of bias. On the other hand, since data already exists, collecting a large sample with long-term follow-up usually requires little effort and resources. Moreover, the information has been collected independent of the study, often reducing the risk of differential classification errors.

A register-based approach is particularly suited for this thesis's research questions. Significantly, it minimizes sampling bias and loss to follow-up, two common issues in clinical research of older adults, especially in those with comorbidity and disability.[120,183] Figure 8 gives an overview of the general strengths and limitations of the included studies. The rest of this chapter will address some points that I think merit extra consideration: i) the issue of confounding, ii) measurement errors, including the epilepsy case definition, iii) missing covariate data, iv) competing risks in time-to-event analysis, and v) ethical considerations.

Strengths	Limitations
Reliable data sources with high coverage	Lack of confounder information
Large sample size – greater precision	Measurement errors
Minimal sampling bias – generalizability	Missing covariate data
Long-term follow-up	
No loss to follow-up (except emigration)	
No differential misclassification	

Figure 8. *Strengths and limitations of the thesis's studies.*

THE ISSUE OF CONFOUNDING

There are several ways to control for confounding, including randomization, restriction, matching, stratification, and adjustments. The first three approaches are applied during data collection, the latter during statistical analysis. In Papers II-IV, we used multivariable regression analyses to adjust the ORs and HRs for various confounders. The controls in Paper II were also matched for age and sex.

A confounding factor distorts the association between the exposure and outcome of interest. For example, in Paper II, we have no way of knowing to what extent the increased OR for stroke depends on the exposure (new-onset seizures) or shared risk factors between the exposure and the outcome (e.g., modifiable vascular risk factors). However, in the particular case of Paper II, the issue of confounding is of less importance, as the purpose of the study was to estimate the risk increase associated with seizures rather than elucidating the mechanisms behind it (which the study design does not allow).

In Papers III-IV, the issue of confounding is all the more important. Due to the register-based approach, we do not know why a specific ASM was chosen. Many factors influence ASM selection, but they also have to be associated with the outcome of interest to become confounders. The selection of covariates for the multivariable models was mainly based on cardiovascular risk factors and stroke characteristics available through the Swedish Stroke Register. An onset with frequent/severe seizures can influence drug choice, thus making it a potential unmeasured confounder in both studies. However, patients treated with carbamazepine had less frequent hospital admissions due to seizures during follow-up (compared to lamotrigine, levetiracetam, and valproic acid, respectively), suggesting the main findings are unlikely to be explained by epilepsy severity.

Considering other unmeasured confounders, it is possible that some non-vascular comorbidities could have influenced ASM choice (due to pharmacokinetics, side effects, or drug-drug interactions). Due to their lower propensity for drug-drug interactions, lamotrigine and levetiracetam would probably be more likely choices than carbamazepine in patients with various comorbidities, for example, malignant neoplasms. I would therefore argue that the net effect of these factors does not explain the difference in mortality between lamotrigine and carbamazepine. In Paper IV, the issue of possible

non-vascular confounders was one of the reasons we decided to analyze the risk of cardiovascular death separately in a competing risk model. Even if such a factor biased the hazard ratios of all-cause death, it would have less impact on cardiovascular death.

MEASUREMENT ERRORS

Measurement errors are more the rule than the exception in register-based research, affecting case ascertainment as well as the classification of exposures and outcomes. Among deceased patients with a prior diagnostic code for epilepsy (G40) in the NPR, 90% fulfill the epilepsy criteria when medical charts are reviewed.[180] Accompanying ASM treatment increases specificity and is often included in case identification algorithms.[157] The validity of the clinical data recorded in the Swedish Stroke Register is high (≥95%) compared to medical charts.[74] However, the definition of poststroke epilepsy, which combines data from several sources, has not been validated yet.

The SPDR has complete coverage of dispensed ASMs but lacks information on the total daily dose and medication compliance. ASM discontinuation required more than one year between dispensations, suggesting a general overestimation of retention rates. The classification of cardiovascular death in the CDR may be incorrect in some cases; compared with medical charts, the level of agreement at ICD chapter level is 87%.[184] The misclassification of exposures and outcomes is non-differential, resulting in conservative estimates.

MISSING COVARIATE DATA

While Papers III-IV had complete information on the exposure and outcomes of interest, some of the covariates included in the multivariable models had missing values. The proportion of missing covariate data was 17% in Paper III and 24% in Paper IV, mainly due to non-response (total or partial) to the Swedish Stroke Register 3-month follow-up.

There are three ways of handling missing covariate data in clinical research: complete-case analysis, imputation, or the missing-indicator method (usually biased in a non-randomized setting).[185] As the missing values were assumed to be missing at random (i.e., can be explained by other available information), imputation is preferable over complete-case analysis to reduce bias and loss of power.[186]

Paper IV used multiple imputation, a method that has gained increasing attention in recent years. Missing values are replaced by multiple sets of imputed values (each set is called an 'imputation'), which are predicted based on the distribution of available data. Each complete data set (Paper IV comprised 20 imputations) is analyzed independently, and then the results are pooled.

To avoid introducing bias, the imputation procedure should include all variables used in the main analysis (including the outcome[187]) and any other variable that may contribute to the prediction of the missing values.[188] Fortunately, our data set included numerous variables from multiple data sources, which could be used to increase the plausibility of the missing at random assumption.

COMPETING RISKS

Censoring is one of the key concepts of time-to-event analysis. A critical assumption for the conventional methods is that censored subjects have the same future risk of the event as those who are still under follow-up (non-informative censoring).[189] As a result, the cumulative incidence may be overestimated when subjects are censored due to a competing event.

When analyzing cardiovascular death in Paper IV, all other causes of death were considered competing risks. As such, Fine-Gray subdistribution hazard regression was used instead of Cox proportional hazards regression. Paper III used conventional survival analysis to analyze the risk of treatment discontinuation. Although death would preclude the event of interest, the subject is not at risk of both events at all times, which means the events compete on unequal terms.[190] Nevertheless, the long-term retention rates may have been underestimated.

ETHICAL CONSIDERATIONS

Register-based studies share ethical issues with other research; examples include data falsification, plagiarism, and conflicts of interest. More general principles also apply, such as that it may be unethical that important research is not carried out or made more difficult for various reasons. It is also an ethical issue if research is of such low quality that it leads to erroneous conclusions.

While register-based research does not entail any physical risk for participants, there may be confidentiality concerns. Particularly, a balance must be struck

between the benefit of the research project and the individual's right to object to having their data shared. When there is no more than minimal risk involved, for instance, when data is securely stored and de-identified, an ethics committee might waive the need for patient consent (Papers I-IV, ethical approval no. 187-15, 2009/355).

Another consideration is that the results may cause concern among people with epilepsy (including other target populations). However, this issue is probably offset by the possibility of improving cardiovascular management and preventing morbidity and mortality in older adults with epilepsy. Nevertheless, a pedagogical challenge can arise when the physician considers treatment with carbamazepine warranted while the patient worries about premature death.

7 CONCLUSIONS

I have argued throughout this work that new-onset seizures in older adults are associated with an increased vascular risk, which must be considered when conducting work-ups and considering ASM treatment. In particular, persons with poststroke epilepsy deserve more ambitious management tailored to their specific needs.

The included studies have contributed findings on long-term clinical outcomes that would be challenging to investigate in traditional clinical trials. Unexplained late-onset seizures were associated with an almost doubled stroke risk, with the highest risk increase in the first year after seizure onset. Presumably, early cardiovascular intervention would reduce long-term morbidity, at least for some patients. It also seems reasonable to avoid enzyme-inducing ASMs, which theoretically can alter cholesterol levels and interfere with drugs that are considered cornerstones of stroke prevention.

Among those with poststroke epilepsy, a subgroup with particularly high vascular risk and potential for drug interactions, more than every third patient was started on a first-generation ASM at the end of the study period (2014). Considering that patients receiving lamotrigine or levetiracetam were more likely to continue treatment than those treated with carbamazepine, it is evident that many patients are not treated optimally. Even more worrisome is that patients treated with carbamazepine or valproic acid had higher all-cause and cardiovascular mortality rates than those receiving lamotrigine. This finding fuels concerns that these ASMs may have clinically relevant effects on vascular risk.

The relevance of this work is underlined by the lack of guidance on how to manage patients with late-onset seizures regarding vascular risk, especially those with a history of cerebrovascular disease. New-onset seizures after middle age seem to warrant cardiovascular evaluation, but it remains unclear how to perform the evaluation and in which cases. I would not recommend widespread vascular screening until more evidence is available. Moreover, first-generation ASMs should be reserved for patients who are difficult to treat. Lamotrigine and levetiracetam seem like equally good first-line treatment options for poststroke epilepsy, although the former may have some limitations due to its slow titration rate.

FUTURE DIRECTIONS

Whether people with late-onset seizures benefit from vascular screening remains debatable. Randomized evidence is probably needed to inform clinical practice, but that would require a large sample and several years of follow-up. To make such a study more feasible, the researcher could use register data for outcomes reporting, simplifying data collection and ensuring minimal loss of follow-up. Large prospective observational studies with information about imaging, vascular risk factors (including lifestyle factors), and ASM treatment are needed to elucidate the mechanisms behind the increased stroke risk.

Regarding treatment with ASMs, several topics require further research. While administrative data on dispensed drugs can be used to estimate retention rates, distinguishing among discontinuation due to inefficacy, poor compliance, or adverse effects is impossible. For this reason, and to rule out residual confounding, an RCT would be valuable. However, due to the increasing awareness of the drawbacks of enzyme induction, randomizing people with poststroke epilepsy to treat them with carbamazepine would be ethically questionable. Instead, a prospective observational study might be a more reasonable approach, especially as it could examine the long-term risk of cerebrovascular events (if powered adequately).

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