INTRODUCTION

Stroke is an important risk factor for epilepsy, and in up to half of all cases with adult-onset epilepsy, the aetiology is a previous stroke. \(^1\) A recent meta-analysis estimated the pooled incidence of post-stroke seizures and post-stroke epilepsy (PSE) to be 7% and 5%, respectively, with no difference in incidence between men and women. \(^2\) In contrast to acute symptomatic seizures which occur within one week of stroke onset, \(^3\) late-onset seizures are considered as unprovoked and is required for the diagnosis of PSE. \(^4,5\) It is rare that PSE occurs later than two years after the stroke. \(^6\) While acute symptomatic seizures have a lower risk of recurrence, the risk of recurrence in late-onset seizures is high, around 70%. \(^7\) Thus,
in PSE, treatment is usually initiated after the first seizure and is lifelong.\textsuperscript{7} Evidence-based guidelines focusing specifically on the management of PSE are lacking.\textsuperscript{4,8-10} A small randomized clinical trial (RCT) published 2007 showed better tolerability for lamotrigine compared to carbamazepine in patients with PSE.\textsuperscript{11} Another RCT in patients with PSE where levetiracetam and carbamazepine were compared found no difference in number of seizure-free patients between the two groups but less side effects in the levetiracetam group.\textsuperscript{12} A Swedish register-based PSE study including patients with stroke 2005-2010 found higher retention rates for levetiracetam and lamotrigine compared to carbamazepine and phenytoin.\textsuperscript{13} PSE has a focal onset and the International League Against Epilepsy (ILAE) has reported “level A” evidence for carbamazepine, levetiracetam, phenytoin and zonisamide for use in focal onset epilepsy in adults.\textsuperscript{14} In elderly, gabapentin and lamotrigine are recommended (level A) as initial monotherapy.\textsuperscript{14}

Treatment changes can be necessary due to side effects or poor seizure control. However, discontinuation may also be explained by poor adherence. In a US study of older persons treated with AED, non-adherence was 37%, and the authors concluded that non-adherence may be more problematic in an older population as the risk of side effects and drug-drug interactions is higher.\textsuperscript{15} Many AEDs have a large potential for interactions with most drug classes, including other AEDs.\textsuperscript{16} This must be considered during combination therapy and concomitant treatment with other drugs, especially for anticoagulants, another common drug class in this patient group.\textsuperscript{17}

Almost one third of stroke patients have atrial fibrillation and are thus treated with oral anticoagulants (OAC).\textsuperscript{18} OAC interact with the cytochrome P450 system, as do most AEDs, which makes the choice of AED challenging.\textsuperscript{19}

With few RCTs and guidelines to steer choice of AED in PSE, observational studies on pharmacological treatment of PSE can further our understanding. Also, few studies on drug treatment in PSE have presented data stratified by sex and even fewer have focussed on sex differences. However, there are reasons to believe that there might be sex differences in first choice of AED and that persistence of different AEDs can vary due to different side effect profiles.\textsuperscript{20,21} The aims of the study were to describe the current use of AEDs when initiating treatment in PSE: which AED is the first choice, how persistence varies between AEDs and if there are any important sex differences.

## METHODS

### 2.1 Data sources

In this observational register study, we used individual-level patient data from the Stockholm regional healthcare data warehouse (VAL). VAL contains encrypted, anonymized data regarding age, sex, diagnoses, hospitalizations, and consultations in hospital-based specialist care (since 1997), consultations in primary care (since 2003) and prescription claims (since July 2010) for all individuals in the urban region of Stockholm (2.4 million inhabitants, March 2020).

### 2.2 Study population

All individuals ≥18 years in the region of Stockholm with a stroke diagnosis (ICD-10 code I60, I61 or I63) as main diagnosis in inpatient care between 1 January 2012 and 31 December 2016, with a first dispensation of any AED (ATC code beginning with N03) up to two years after the stroke diagnosis, were identified from the database. First dispensation was defined as not having been dispensed any AED up to one year before stroke diagnosis. From this group, we selected all individuals with an epilepsy-related diagnosis (ICD-10 code G40, G41, R25 or R56) recorded in in- or outpatient care after the stroke and before the first dispensation of AED to constitute the study population. The selection procedure to identify the study population is described in Figure 1.

For individuals with more than one recorded stroke diagnosis within the study period, analysis was restricted to the first diagnosis that met the inclusion criteria. Individuals with epilepsy-related diagnosis up to 2 years before the stroke were excluded. Individuals diagnosed with epilepsy during the same hospitalization as their stroke were excluded if the hospitalization time was shorter than 8 days, assuming the seizures to be acute symptomatic. Also, individuals who moved to the Stockholm region less than two years before their index stroke were excluded, in order to have a medical history of at least two years in data.

Dispensation of AEDs was followed until 31 December 2019. Thus, the follow-up period could be from 1 to 8 years. Patients who died or moved from the region during the follow-up period were censored in the persistence analysis.

### 2.3 Study variables

Baseline patient characteristics include age, sex and stroke type. Data on comorbidities recorded in in- or outpatient care up to 2 years before first dispensation of AED, as well as treatment with antihypertensives or OAC up to 1 year before first dispensation of AED, were retrieved from the database. Definitions with ICD-10 codes and ATC codes are presented in Appendix (Table S1).

Number of different drugs (substances) dispensed up to one year before first dispensation of AED was counted as well as number of days in inpatient care, days with visits in special care and days with primary care visits to a physician.
2.4 Statistical analysis

Baseline characteristics are presented as frequencies and percentages for categorical variables, and as mean values and standard deviation (SD) for continuous variables. Descriptive statistics were used to describe number and proportions of new users of each AED in men and women, respectively.

Multinomial logistic regression analysis was used to identify factors associated with first choice of AED. This method was used since multiple response outcomes were studied. In our model, choice of AED (levetiracetam, carbamazepine, lamotrigine, valproic acid and other AED/combination) was considered as dependent variable and levetiracetam was the reference category. All baseline patient variables as well as year of first AED dispensation were tested in a univariable model, and variables with a p-value <0.1 were included in the multivariable model. Continuous variables measuring general consumption of healthcare were split by tertiles into three categories: number of substances dispensed: 0-7 (reference), 8-12 and 13-43; number of days in inpatient care: 0-18 (reference), 19-40, and 41-217; number of days with a specialist consultation: 1-3 (reference), 4-6, and 7-34; number of days with consultation to a primary care physician: 0-1 (reference), 2-5 and 6-49; number of days from stroke to AED: 8-116 (reference), 117-321 and 322-730.

Persistence to first AED dispensed was measured in each patient with the time calculated from treatment start, defined as first dispensation date, to treatment end, with censoring at longer hospitalization (>1 month), migration, death or at the end of follow-up, whichever came first. In Sweden, each prescription is valid for 1 year and prescription medicines are funded through a national pharmaceutical benefits scheme allowing each patient to purchase medicines for 3 months’ supply at a time. Consequently, patients with medications for chronic use are assumed to purchase their medicines about every ninety to one hundred days, and we classified patients with a gap of >120 days between two claims as non-persistent. This has been used previously in stroke studies analysing persistence. In recent years, an increasing number of patients use multi-dose drug dispensing. For these patients, oral medications for chronic use are machine-dispensed together into disposable sachets for each dose occasion. Each sachet is individually marked with patient data, drug contents data and time for administration. Usually, one delivery contains medication for 14 days. For patients with multi-dose drug dispensing, we applied a gap of >21 days to assess persistence. The stop date at non-persistence was defined as the date of the last dispensation with an addition of 90 days for ordinary prescriptions and 14 days for multi-dose drug dispensing. Individuals who changed AED or received addition of another AED were classified as non-persistent. Persistence was plotted using Kaplan-Meier survival curves.

Logistic regression analysis was used to identify factors associated with the risk of treatment discontinuation within 90 days (which corresponds to a single dispensation of a prescription). All baseline patient variables and year of first AED dispensation were included in the model. The continuous variables measuring general consumption of health care were categorized in the same way as they were in the multinomial logistic regression analysis. Significance was assumed at P-value <.05.

Data management and statistical analyses were performed using SAS EG 8.2 (SAS Institute Inc), R version 3.5.1 (R Core Team) and Stata version 11 (StataCorp).
In all, 9,652 men and 9,844 women with a stroke diagnosis were identified. Of these 560 patients, 3.0% of the men and 2.8% of the women fulfilled the inclusion criteria. Baseline characteristics for these patients are described in Table 1. Of the study population, 64% (55% of men and 74% of women, respectively) used multi-dose drug dispensing during follow-up. Of the 560 patients fulfilling the criteria, 57 (33 men, 24 women) had index stroke and the first registered diagnosis of epilepsy during the same care period. Of these, eight individuals had time to treatment discontinuation less than 90 days, indicating treatment for acute symptomatic seizure. In all, 21 persons (seven men, 14 women) had a diagnosis of status epilepticus (G41) alone or in combination before dispensation of first AED.

The most common AED used for initiation of therapy was levetiracetam followed by carbamazepine (Table 2). More than 80% of both men and women started antiepileptic treatment with one of these drugs.

Patient sex and age, renal impairment, hospitalization due to epilepsy before AED, and number of days from stroke to AED were each associated with the choice of at least one AED (Table 3). Lamotrigine was more often chosen in women than in men, and valproic acid was less used in women than in men.

Persistence did not differ substantially between men and women for any of the four most used drugs. Comparing the individual drugs, levetiracetam had the highest persistence in both men and women. The Kaplan-Meyer curves for the four most used AEDs are presented in Figure 2. The persistence for levetiracetam after one year was 51% in men and 58% in women, and after two years, 28% in men and 35% in women, respectively. This was higher than for carbamazepine.
lamotrigine and valproic acid. The overall persistence measured as dispensation of any AED after one year was 56% in men and 57% in women, and after two years, 38% in men and 41% in women.

Choice of AED, concomitant OAC treatment and percutaneous endoscopic gastrostomy (PEG) was associated with discontinuation of AED within 90 days (Table 4). Individuals with carbamazepine as well as other AED/combination had increased risk of treatment discontinuation as compared to individuals with levetiracetam. Individuals treated with OAC and individuals with PEG had decreased risk of treatment discontinuation.

4 | DISCUSSION

In this population-based study of all patients with PSE in a large urban region of 2.4 million inhabitants, we found levetiracetam to be the most used AED for initiation of therapy in both men and women. Levetiracetam was also the drug the patients continued to use to the highest degree. There were some minor sex differences in the use of AED, but no difference in persistence. Several factors, including sex, age and renal impairment, were associated with choice of AED. Only three factors though, choice of AED, use of OAC and PEG, showed an association with persistence to therapy.

We estimated the proportion of stroke patients with AED treated PSE to 3.0% and 2.8% of men and women, respectively, which is similar or lower than described in other studies. This may be explained by differences in definition of epilepsy in different studies and the lack of a uniform definition on how to identify these patients in registers. The vast majority of the individuals who were excluded from the study population since they had no diagnosis of epilepsy were initiated on treatment with either gabapentin or pregabalin. This suggests that the treatment was probably used for other indications, such as neuropathic pain conditions and fibromyalgia.

Levetiracetam was the most common AED, followed by carbamazepine in both men and women. In men, valproic acid came third and lamotrigine came forth. In women, lamotrigine was more common than valproic acid. The choice of AED for initiation in our study differs from an older Taiwanese study where most of the patients with PSE (69%) had been prescribed phenytoin, followed by valproic acid, new AEDs (including levetiracetam and lamotrigine) and carbamazepine. However, these data were from 2004 to 2008, and the prescribing pattern for AEDs may change over time and no sex-specific data were presented. In a Swedish observational study of PSE based on data from 2005 to 2010, carbamazepine was the most used AED, used by nearly half of both men and women. In men, it was followed by valproic acid, levetiracetam and lamotrigine, in women by valproic acid, lamotrigine and levetiracetam. During the study period, levetiracetam replaced carbamazepine as the most common prescribed first AED. Our study, which is performed five years later, shows that levetiracetam remained the most common first choice during the study period. Similar findings were shown by Fox et al who studied trends in AED use among elderly patients with epilepsy in the USA. Both levetiracetam and valproic acid are AEDs that are used in status epilepticus. Less than 4% (21/560) of our cohort had a diagnosis of status epilepticus registered before first dispensation of AED. Thus, it is unlikely that presence of status epilepticus had any obvious influence on treatment choice.

PSE is most common in the elderly, in whom the tolerability of AEDs may be lower due to age-related changes in pharmacokinetics and pharmacodynamics, comorbidities and simultaneous use of potentially interacting drugs. With a mean age of 69.7 years in men and 76.3 years in women, the use of levetiracetam is in line with the results from a post hoc subgroup analysis of patients ≥60 years in a RCT where levetiracetam is suggested as a suitable option for initial monotherapy for elderly patients with newly diagnosed epilepsy.

Women had higher probability to initiate treatment with lamotrigine than men and lower probability to initiate treatment with valproic acid. Although our study population was elderly and not of childbearing potential, the concept of avoiding valproic acid in women may be ingrained in prescribers. Also, the risk of hyperammonemia and encephalopathy from

|                  | Men, n (%) | Women, n (%) | P    |
|------------------|------------|--------------|------|
| Levetiracetam    | 177 (61.7) | 175 (64.1)   | .552 |
| Carbamazepine    | 66 (23.0)  | 51 (18.7)    | .209 |
| Lamotrigine      | 9 (3.1)    | 20 (7.3)     | .035 |
| Valproic acid    | 20 (7.0)   | 7 (2.6)      | .017 |
| Phenytoin        | 5 (1.7)    | 4 (1.5)      | 1.000|
| Combination with levetiracetam* | 5 (1.7) | 7 (2.6) | .569 |
| Other AED/other combination ** | 5 (1.7) | 9 (3.3) | .286 |

*Combination with levetiracetam and one other AED (carbamazepine/phenytoin/gabapentin/valproic acid); **Clonazepam/gabapentin/lacosamide/pregabalin/lorzepam+lamotrigine.
| Reference, Levetiracetam | Carbamazepine | Lamotrigine | Valproic acid | Other AED/combination |
|--------------------------|----------------|-------------|---------------|----------------------|
|                          | Adjusted RRR (95% CI) | P | Adjusted RRR (95% CI) | P | Adjusted RRR (95% CI) | P | Adjusted RRR (95% CI) | P |
| Sex                      |                |    |                |    |                |    |                |    |
| Male                     | 1              | .26 | 2.58 (1.02-6.54) | .046 | 0.28 (0.10-0.76) | .01 | 1.35 (0.59-3.09) | .48 |
| Female                   | 0.76 (0.47-1.23) | .26 |                |    |                |    |                |    |
| Age group                |                |    |                |    |                |    |                |    |
| 18-64                    | 1              | .10 | 0.44 (0.13-1.50) | .19 | 4.36 (0.77-24.77) | .10 | 0.15 (0.05-0.46) | .001 |
| 65-79                    | 0.57 (0.29-1.11) | .10 | 0.44 (0.12-1.70) | .24 | 7.43 (0.75-30.11) | .10 | 0.24 (0.08-0.77) | .02 |
| 80+                      | 0.69 (0.33-1.42) | .31 |                |    |                |    |                |    |
| Comorbidities            |                |    |                |    |                |    |                |    |
| Atrial fibrillation      | 0.64 (0.34-1.18) | .15 | 0.52 (0.17-1.64) | .27 | 2.53 (0.81-7.90) | .11 | 1.62 (0.55-4.77) | .38 |
| Renal impairment         | 1.22 (0.58-2.56) | .60 | 0.47 (0.09-2.42) | .37 | 6.15 (2.11-17.92) | .001 | 0.23 (0.03-1.98) | .18 |
| Other drug treatment     |                |    |                |    |                |    |                |    |
| Antihypertensive         | 1.28 (0.65-2.52) | .48 | 0.54 (0.16-1.81) | .32 | 0.49 (0.12-2.01) | .32 | 0.61 (0.22-1.66) | .33 |
| OAC                      | 0.61 (0.31-1.19) | .15 | 1.49 (0.49-4.50) | .48 | 0.37 (0.10-1.33) | .13 | 0.96 (0.33-2.77) | .94 |
| Hospitalization due to epilepsy before AED | 0.92 (0.55-1.54) | .75 | 1.82 (0.59-5.61) | .30 | 0.75 (0.27-2.05) | .58 | 0.17 (0.07-0.41) | .00 |
| Days from stroke to AED  |                |    |                |    |                |    |                |    |
| 8-116                    | 1              | .18 | 6.20 (1.60-24.06) | .008 | 1.35 (0.39-4.66) | .64 | 1.40 (0.46-4.27) | .55 |
| 117-321                  | 1.52 (0.83-2.79) | .18 |                |    |                |    |                |    |
| 322-730                  | 1.11 (0.57-2.15) | .75 | 1.50 (0.33-6.96) | .60 | 0.94 (0.25-3.53) | .92 | 3.08 (1.11-8.55) | .03 |
| Days in inpatient care   |                |    |                |    |                |    |                |    |
| 0-18                     | 1              | .07 | 0.57 (0.20-1.66) | .30 | 3.43 (0.77-15.33) | .11 | 2.22 (0.79-6.24) | .13 |
| 19-40                    | 1.74 (0.95-3.18) | .07 |                |    |                |    |                |    |
| 41-217                   | 1.40 (0.74-2.64) | .30 | 0.56 (0.12-1.09) | .12 | 4.84 (1.02-23.03) | .048 | 1.50 (0.51-4.42) | .46 |
| Days with specialist consultation(s) | 0.74 (0.40-1.35) | .32 | 0.96 (0.24-3.73) | .95 | 0.12 (0.03-0.58) | .01 | 1.10 (0.39-3.05) | .86 |
| 1-3                      | 1              | .31 | 1.96 (0.53-7.17) | .31 | 0.76 (0.24-2.46) | .65 | 0.95 (0.31-2.89) | .93 |
| 4-6                      | 1.00 (0.53-1.86) | .99 |                |    |                |    |                |    |
| Number of dispensed substances |                |    |                |    |                |    |                |    |
| 0-7                      | 1              | .69 | 1.32 (0.35-4.96) | .68 | 0.66 (0.17-2.55) | .55 | 1.47 (0.54-4.01) | .45 |
| 8-12                     | 1.14 (0.61-2.13) | .69 |                |    |                |    |                |    |
| 13-43                    | 1.55 (0.81-2.99) | .19 | 3.41 (0.94-12.41) | .06 | 1.20 (0.30-4.76) | .80 | 1.94 (0.63-5.98) | .25 |
| Year index AED           |                |    |                |    |                |    |                |    |
| 2012                     | 1.69 (0.80-3.57) | .17 | 0.63 (0.11-3.78) | .61 | 4.92 (1.15-21.03) | .03 | 0.86 (0.15-4.88) | .86 |
| 2013                     | 1              | .17 |                |    |                |    |                |    |
| 2014                     | 0.40 (0.20-0.79) | .008 | 0.34 (0.10-1.24) | .10 | 1.01 (0.19-5.40) | .99 | 0.66 (0.21-2.10) | .49 |
| 2015                     | 0.32 (0.16-0.64) | .001 | 0.67 (0.22-2.08) | .49 | 1.02 (0.22-4.82) | .98 | 0.72 (0.21-2.42) | .59 |
| 2016                     | 0.25 (0.12-0.53) | <.001 | 0.39 (0.11-1.39) | .15 | 0.56 (0.10-3.14) | .51 | 0.57 (0.17-1.87) | .35 |
| 2017                     | 0.14 (0.05-0.45) | .001 | 0.13 (0.02-1.18) | .07 | 2.81 (0.55-14.23) | .21 | 0.44 (0.10-2.01) | .29 |
| 2018                     | 0.74 (0.13-4.29) | .73 | 0.00 (0.00) | .99 | 0.00 (0.00) | .98 | 1.57 (0.13-19.49) | .72 |

Note: Bold values indicate statistically significant findings (P < .05).
Abbreviations: CI, confidence interval; OAC, oral anticoagulant; RRR, relative risk ratio.
Valproic acid treatment has been suggested to be higher in women. Albeit, there are studies showing men to have a higher risk.

No association between choice of AED and concomitant treatment with OAC was found. This was rather unexpected as several AEDs interact with OACs by inducing activity of CYP3A4 and the drug transporter P-glycoprotein (P-gp). Levetiracetam which has low interaction potential, particularly compared with the strong CYP inducer carbamazepine, has been considered as a good choice. In 2018 though, The European Heart Rhythm Association cautioned prescribers for interactions not only with the stronger CYP inducers but also with levetiracetam based on the risk of interaction on P-gp level. Even though this recommendation has been criticized as it is based on animal data and not supported in clinical data, it may explain our finding.

Persistence of AED is usually dependent on a combination of efficacy and tolerability. As the persistence analysis performed in the present study covers a short period of time, it may primarily reflect tolerability and to a lesser extent efficacy. A review by Xu from 2018 concluded that levetiracetam and lamotrigine were the best tolerated AEDs in treatment of PSE, as well as other types of epilepsy in elderly patients. However, a meta-analysis by Zaccara et al showed relevant differences in short-term tolerability between different AEDs. Brivaracetam, gabapentin and levetiracetam had the best tolerability profile. This in spite of levetiracetam having a risk of adverse effects such as irritability, mood disorders and depression, which limits its use. None of the studies presented their results stratified by sex.

We acknowledge that our study has some weaknesses. Register-based studies may have problems of poor validity of the diagnoses and incomplete data. However, the validity of the epilepsy diagnosis (G40) has been estimated to slightly above 90% in the Swedish National Patient Register (NPR), the same data source as our data. In this study, we tried to manage confounding by adjusting for baseline characteristics. However, residual confounding is possible.
since choice of AED as well as persistence can be affected by other unmeasured factors. Consequently, randomization would be required to assess to what extent the drugs differ in tolerability. Also, we do multiple comparisons which may introduce a risk of chance findings. Furthermore, due to the design of the study, we cannot differentiate on the presence of acute symptomatic seizures if the patient had a recurrent stroke. Even though the Swedish stroke register, Riksstroke, recommends that the stroke diagnosis codes of I61 or I63 are only used for acute stroke, the codes can be used for up to a year after stroke onset. 40 Thus, it is difficult to differentiate between a recurrent stroke within a year of the previous one. However, we also believe our study to have strengths. We included data from all hospitals and primary care centres in a large region with a population-based, state-subsidized health system covering all inhabitants. Besides, we present all data separately for men and women, which has only been done in a limited number of RCTs and observational studies on PSE treatment. Furthermore, we included patients with multi-dose drug dispensing, a group often excluded in persistence studies conducted in Sweden. 41 Interestingly, the majority of our study population used multi-dose drug dispensing during follow-up. As the population using multi-dose drug dispensing is older, have more polypharmacy and more comorbidities, 42,43 excluding this group may add a

### TABLE 4

Factors associated with discontinuation of AED within 90 d, logistic regression

| First dispensed AED | Adjusted OR (95% CI) | P   |
|---------------------|----------------------|-----|
| Levetiracetam       | 1                    |     |
| Carbamazepine       | 2.20 (1.30-3.73)     | .003|
| Lamotrigine         | 1.13 (0.41-3.10)     | .81 |
| Valproic acid       | 1.83 (0.64-5.23)     | .26 |
| Other AED/combination | 4.64 (2.07-10.41) | <.001|

| Sex                | Adjusted OR (95% CI) | P   |
|--------------------|----------------------|-----|
| Male               | 1                    |     |
| Female             | 0.98 (0.61-1.56)     | .93 |

| Age group          | Adjusted OR (95% CI) | P   |
|--------------------|----------------------|-----|
| 18-64              | 1                    |     |
| 65-79              | 0.82 (0.43-1.57)     | .55 |
| 80+                | 1.09 (0.54-2.22)     | .81 |

| Stroke type        | Adjusted OR (95% CI) | P   |
|--------------------|----------------------|-----|
| I63 Cerebral infarction | 1                |     |
| I60 Non-traumatic subarachnoid haemorrhage | 1.20 (0.39-3.68) | .76 |
| I61 Non-traumatic intracerebral haemorrhage | 1.26 (0.71-2.26) | .43 |

| Comorbidities      | Adjusted OR (95% CI) | P   |
|--------------------|----------------------|-----|
| Atrial fibrillation | 1.09 (0.61-1.95)     | .76 |
| Dementia           | 0.47 (0.21-1.07)     | .07 |
| Neuropathic pain   | 1.03 (0.66-1.62)     | .89 |
| PEG                | 0.34 (0.13-0.88)     | .03 |
| Psychiatric conditions | 0.90 (0.49-1.65) | .73 |
| Renal impairment   | 1.01 (0.49-2.09)     | .98 |

| Other drug treatment | Adjusted OR (95% CI) | P   |
|----------------------|----------------------|-----|
| Antihypertensive     | 1.37 (0.71-2.63)     | .35 |
| OAC                  | 0.50 (0.26-0.96)     | .04 |

| Hospitalization due to epilepsy before AED | Adjusted OR (95% CI) | P   |
|-------------------------------------------|----------------------|-----|
| 1.17 (0.71-1.94)                          | .53                  |

| Days from stroke to AED                  | Adjusted OR (95% CI) | P   |
|------------------------------------------|----------------------|-----|
| 8-116                                     | 1                    |     |
| 117-321                                   | 1.36 (0.75-2.48)     | .31 |
| 322-730                                   | 1.54 (0.83-2.84)     | .17 |

| Days in inpatient care                   | Adjusted OR (95% CI) | P   |
|------------------------------------------|----------------------|-----|
| 0-18                                     | 1                    |     |
| 19-40                                    | 0.71 (0.40-1.25)     | .24 |
| 41-217                                   | 0.93 (0.51-1.69)     | .81 |

| Days with specialist consultation(s)    | Adjusted OR (95% CI) | P   |
|------------------------------------------|----------------------|-----|
| 1-3                                      | 1                    |     |

### TABLE 4 (Continued)

Day index AED

| Year AED | Adjusted OR (95% CI) | P   |
|----------|----------------------|-----|
| 2012     | 0.64 (0.28-1.44)     | .28 |
| 2013     | 1                    |     |
| 2014     | 0.65 (0.33-1.27)     | .20 |
| 2015     | 0.80 (0.41-1.55)     | .50 |
| 2016     | 0.67 (0.33-1.37)     | .27 |
| 2017     | 0.42 (0.17-1.06)     | .07 |
| 2018     | 0.36 (0.06-2.27)     | .28 |

Number of dispensed substances

| Number of dispensed substances | Adjusted OR (95% CI) | P   |
|--------------------------------|----------------------|-----|
| 0-7                            | 1                    |     |
| 8-12                           | 1.09 (0.60-1.97)     | .78 |
| 13-43                          | 1.24 (0.65-2.36)     | .52 |

Note: Bold values indicate statistically significant findings (P < .05).

Abbreviations: CI, confidence interval; OAC, oral anticoagulant; OR, relative risk ratio; PEG, percutaneous endoscopic gastrostomy.
substantial bias. Multi-dose drug dispensing may contribute to a higher persistence and influence the choice of drugs. However, this is impossible to elucidate from a register-based study given the large number of confounders. In this vulnerable patient group, randomized, controlled trials are challenging to conduct and observational studies as ours can contribute with important knowledge.

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CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
MvE initiated the study and introduced the research question. All authors participated in designing the study. DL and LL performed the data extractions. DL, LL and AS conducted the analyses. All authors discussed the results. DL wrote the manuscript, and all authors reviewed and edited it. All authors accepted the final version of the manuscript.

ETHICAL APPROVAL
The study was approved by the regional ethics committee in Stockholm, Sweden (Ref. no. 2015/660-31 and amendment 2019-03564).

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REFERENCES
1. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. Lancet Neurol. 2009;8(11):1019-1030. https://doi.org/10.1016/s1474-4242(09)70240-6
2. Zou S, Wu X, Zhu B, Yu J, Yang B, Shi J. The pooled incidence of post-stroke seizure in 102 008 patients. Top Stroke Rehabil. 2015;22(6):460-467. https://doi.org/10.1179/1074935715z.0000000062
3. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010;51(4):671-675. https://doi.org/10.1111/j.1528-1167.2009.02285.x
4. Wang JZ, Vyas MV, Saposnik G, Burneo JG. Incidence and management of seizures after ischemic stroke: Systematic review and meta-analysis. Neurology. 2017;89(12):1220-1228. https://doi.org/10.1212/wnl.000000000004407
5. Zhao Y, Li X, Zhang K, Tong T, Cui R. The progress of epilepsy after stroke. Curr Neuropharmacol. 2018;16(1):71-78. https://doi.org/10.2174/1570159x16666170613083253
6. Guo J, Li J, Zhou M, et al. Statin treatment reduces the risk of poststroke seizures. Neurology. 2015;85(8):701-707. https://doi.org/10.1212/wnl.000000000001814
7. Zelano J, Holtkamp M, Agarwal N, Lattanzi S, Trinka E, Brigo F. How to diagnose and treat post-stroke seizures and epilepsy. Epileptic Disord. 2020;22(3):252-263. https://doi.org/10.1684/epd.2020.1159
8. Holtkamp M, Beghi E, Benninger F, Kälviäinen R, Rocamora R, Christensen H. European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. Eur Stroke J. 2017;2(2):103-115. https://doi.org/10.1177/2396987317705536
9. Sykes L, Wood E, Kwan J. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database Syst Rev. 2014;24(1):CD005398. https://doi.org/10.1002/14651858.CD005398.pub3
10. Gilad R. Management of seizures following a stroke: what are the options? Drugs Aging. 2012;29(7):533-538. https://doi.org/10.2165/11631540-000000000-00000
11. Gilad R, Sadeh M, Rapoport A, Dabby R, Boaz M, Lampy Y. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol. 2007;30(4):189-195. https://doi.org/10.1097/WNF.0b013e318033069
12. Consoli D, Bosco D, Postorino P, et al. Levetiracetam versus carbamazepine in patients with late poststroke seizures: a multicenter prospective randomized open-label study (EpIC Project). Cerebrovasc Dis. 2012;34(4):282-289. https://doi.org/10.1159/000342669
13. Larsson D, Asberg S, Kumlien E, Zelano J. Retention rate of first antiepileptic drug in poststroke epilepsy: A nationwide study. Seizure. 2019;64:29-33. https://doi.org/10.1016/j.seizure.2018.11.013
14. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54(3):551-563. https://doi.org/10.1111/epi.12074
15. Piper K, Richman J, Faught E, et al. Adherence to antiepileptic drugs among diverse older Americans on Part D Medicare. Epilepsy Behav. 2017;66:68-73. https://doi.org/10.1016/j.yebeh.2016.10.017
16. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord. 2014;16(4):409-431. https://doi.org/10.1684/epd.2014.0714
17. Taha M, Li W, Schmidt CM, Gonzalez-Castellon M, Taraschenko O. The interactions between anticonvulsants and non-vitamin K antagonist oral anticoagulant agents: a systematic review. Epilepsy Res. 2020;162:106304. https://doi.org/10.1016/j.eplepsyres.2020.106304
18. Riksstroke. Arrsrapport Stroke och TIA. 2019 2020. http://www. riksstroke.org/wp-content/uploads/2020/09/Riksstroke_Arrsrapport-2019_slutfersionWEB-1.pdf
19. Steffl J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330-1393. https://doi.org/10.1093/eurheartj/ehy136
20. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol. 2012;11(9):792-802. https://doi.org/10.1016/S1474-4242(12)70153-9
21. Bafitau A, Lima MH, Svendsen K, Larsson PG, Johannessen SI, Landmark CJ. Safety aspects of antiepileptic drugs—a population-based study of adverse effects relative to changes in utilisation. Eur J Clin Pharmacol. 2019;75(8):1153-1160. https://doi.org/10.1007/s00228-019-02678-1
22. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010;41(2):397-401. https://doi. org/10.1161/strokeaha.109.566950
23. Bardage C, Ekedahl A, Ring L. Health care professionals’ perspectives on automated multi-dose drug dispensing. Pharm Pract...
24. Slapo GD, Lossius MI, Gjerstad L. Poststroke epilepsy: occurrence, predictors and treatment. Expert Rev Neurother. 2006;6(12):1801-1809. https://doi.org/10.1586/14737175.6.12.1801

25. Huang YH, Chi NF, Kuan YC, et al. Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of late-onset post-stroke epilepsy in Taiwan. Eur J Neurol. 2015;22(11):1459-1468. https://doi.org/10.1111/ejne.12766

26. Fox J, Ajinkya S, Lekoubou A. Patterns of antiepileptic drug use among elderly patients with epilepsy: 2004–2015. Epilepsy Res. 2020;161:106297. https://doi.org/10.1016/j.eplepsyr.2020.106297

27. Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: A systematic review and network meta-analysis. Epilepsy Behav. 2019;101:106466. https://doi.org/10.1016/j.yebeh.2019.106466

28. Perucca E, Berlowitz D, Birnbaum A, et al. Pharmacological and clinical aspects of antiepileptic drug use in the elderly. Epilepsy Res. 2006;68(Suppl 1):S49-S63. https://doi.org/10.1016/j.eplepsyr.2005.07.017

29. Pohlmann-Eden B, Marson AG, Noack-Rink M, et al. Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study. BMC Neurol. 2016;16(1):149. https://doi.org/10.1186/s12883-016-0663-7

30. Yamamoto Y, Takahashi Y, Imai K, et al. Risk factors for hyperammonemia in pediatric patients with epilepsy. Epilepsia. 2013;54(6):983-989. https://doi.org/10.1111/epi.12125

31. Yamamoto Y, Takahashi Y, Suzuki E, et al. Risk factors for hyperammonemia associated with valproic acid therapy in adult epilepsy patients. Epilepsy Res. 2012;101(3):202-209. https://doi.org/10.1016/j.eplepsyr.2012.04.001

32. Tseng YL, Huang CR, Lin CH, et al. Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy. Medicine. 2014;93(11):e66. https://doi.org/10.1097/MD.000000000000066

33. Mathy FX, Dohin E, Bonfitto F, Pelgrims B. Drug-drug interaction between levetiracetam and non-vitamin K antagonist anticoagulants. Eur Heart J. 2019;40(19):1571. https://doi.org/10.1093/eurheartj/ehy780

34. Xu MY. Poststroke seizure: optimising its management. Stroke Vasc Neurol. 2019;4(1):48-56. https://doi.org/10.1136/svn-2018-000175

35. Werhahn KJ, Trinka E, Dobesberger J, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia. 2015;56(3):450-459. https://doi.org/10.1111/epi.12926

36. Zaccara G, Giovannelli F, Giorgi FS, Franco V, Gasparini S, Benedetto U. Tolerability of new antiepileptic drugs: a network meta-analysis. Eur J Clin Pharmacol. 2017;73(7):811-817. https://doi.org/10.1007/s00228-017-2245-z

37. European Medicines Agency. Keppra. Accessed Aug 17, 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/keppra

38. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol. 1996;25(2):435-442.

39. Sveinsson O, Andresson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. Neurology. 2017;89(2):170-177. https://doi.org/10.1212/wnl.0000000000004094

40. Register RTSS. Riksstrokes diagnoslathund. 2019.

41. Wallerstedt SM, Wettermark B, Hoffmann M. The first decade with the Swedish Prescribed Drug Register - a systematic review of the output in the scientific literature. Basic Clin Pharmacol Toxicol. 2016;119(5):464-469. https://doi.org/10.1111/bcpt.12613

42. Caleres G, Modig S, Midlöv P, Chalmers J, Bondesson Å. Medication discrepancies in discharge summaries and associated risk factors for elderly patients with many drugs. Drugs Real World Outcomes. 2020;7(1):53-62. https://doi.org/10.1007/s40801-019-00176-5

43. Morin L, Johnell K, Larooche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. Clin Epidemiol. 2018;10:289-298. https://doi.org/10.2147/cepl.S153458

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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