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Anticonvulsant primary and secondary prophylaxis for acute ischemic stroke patients: a decision analysis

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Abstract

Background and Purpose: We examined the impact of three anticonvulsant prophylaxis strategies on quality-adjusted life years (QALY) among patients with an incident acute ischemic stroke (AIS).

Methods: We created a decision tree to evaluate three strategies: 1) long-term primary prophylaxis; 2) short-term secondary prophylaxis after an early seizure with lifetime prophylaxis if persistent or late seizures developed; and 3) long-term secondary prophylaxis if either early, late, or persistent seizures developed. The outcome was quality-adjusted life expectancy (QALY). We created four base cases to simulate common clinical scenarios: 1) female patient aged 40 with a 2% or 11% lifetime risk of a late seizure and a 33% lifetime risk of an adverse drug reaction (ADR); 2) male aged 65 with a 6% or 29% late seizure risk, and 60% ADR risk; 3) male aged 50 with an 18% or 65% late seizure risk and 33% ADR risk; and 4) female aged 80 with a 29%

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SUPPLEMENTAL MATERIAL
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Online Table I
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or 83% late seizure risk and 80% ADR risk. In sensitivity analyses we altered the parameters and assumptions.

Results: Across all four base cases, primary prophylaxis yielded the fewest QALYs when compared with secondary prophylaxis. For example, under scenario 1, strategies 2 and 3 resulted in 7.17 QALYs each, but strategy 1 yielded only 6.91 QALYs. Under scenario 4, strategies 2 and 3 yielded 2.85 QALYs compared with 1.40 QALYs for strategy 1. Under scenarios in which patients had higher ADR risks, strategy 2 led to the most QALYs.

Conclusions: Short-term therapy with continued anticonvulsant prophylaxis only after post-ischemic stroke seizures arise dominates lifetime primary prophylaxis in all scenarios examined.

Our findings reinforce the necessity of close follow-up and discontinuation of anticonvulsant seizure prophylaxis started during AIS hospitalization.

Keywords

Stroke; Seizure; Decision Trees

INTRODUCTION

Post-stroke seizures are a common sequela of acute ischemic stroke (AIS). Among adult patients admitted for AIS, the pooled incidence of early seizure (acute symptomatic; ≤7 days following AIS) is estimated between 3–4%, and the incidence rate for unprovoked late seizures (unprovoked; >7 days following AIS) is estimated at 18 per 1,000 person-years.[1] Seizures in this population result in increased hospitalization,[2] higher healthcare spending,[3] higher morbidity,[3] and poorer quality of life (QOL).[4]

Guidelines for post-stroke seizure management, however, are limited due to a dearth of randomized clinical trials and the optimal seizure prophylaxis strategy after AIS remains uncertain.[1] Physicians might prescribe short- or long-term secondary prophylaxis after early seizures, and long-term secondary prophylaxis after late seizures for patients with AIS. With the advent of newer generation anticonvulsants that could have a better safety profile, and of prediction models to stratify AIS patients at risk for post-stroke epilepsy, many could be tempted to use anticonvulsant therapy more aggressively or for a broader range of patients. Unfortunately, there are no trial data guiding therapy at this point, nor are there any trials close to completion.[5] Given the limited evidence base, simulation via a decision analysis could best incorporate current knowledge and evaluate the tradeoffs associated with potential treatment strategies.

This decision analysis evaluates the net benefit of three plausible prophylaxis strategies: (1) long-term primary seizure prophylaxis; (2) short-term secondary prophylaxis after early seizure, long-term prophylaxis after late seizure; (3) long-term secondary prophylaxis after early seizure. We compared the three strategies under multiple scenarios in which we altered the risks of adverse events associated with both treatment and failure to treat.

METHODS

We have included all data analyzed during the current study in this manuscript or supplemental material.

We used TreeAge Pro Healthcare (Williamstown, MA) to create a decision tree (Figure 1) and conduct our analyses. We modeled the management of adult patients aged 18+ years, without prior history of epilepsy or stroke, presenting with an incident acute ischemic stroke (AIS). The tree starts with the patient's admission to the hospital due to a newly diagnosed AIS with lifetime follow-up as estimated by age-specific life expectancy.[6] The tree includes estimated probabilities and QOL utility values for the occurrence of early seizures, late seizures, refractory seizures (RS), anticonvulsant-related adverse-drug reactions (ADR), and anticonvulsant efficacy on preventing seizures based on published data. Our main outcome was the number of quality adjusted life years (QALY), defined as the sum across all events of the product of the utility score (QOL) and the life expectancy associated with each event. The preferred treatment strategy was the one that yielded the most QALYs. We considered four clinical scenarios with which to evaluate the competing prophylaxis strategies: 1) a patient with low late seizure risk, average ADR risk and ADR utility; 2) a patient with low-intermediate late seizure risk, high ADR risk, and low ADR utility; 3) a patient with high late seizure risk, average ADR risk and ADR utility; and 4) a patient with high late seizure risk, high ADR risk, and very low ADR utility.

Model Strategies

We evaluated three anticonvulsant prophylaxis strategies that reflect the plausible range of approaches.

Strategy 1: Long-term Primary Prophylaxis

Patients receive an anticonvulsant before presenting with any seizures during the index hospitalization and remain on therapy for life. This strategy represents a plausible comparator for the other strategies that has not been assessed in clinical trials. Additionally, it arguably represents a plausible de facto strategy in which a patient has a brief spell of neurologic dysfunction and the possibility of seizure is raised but not confirmed, and an anticonvulsant is prescribed "just in case" with the sense that it is a relatively low risk medication, and outpatient physicians perpetuate prescriptions started during a hospital admission.

Strategy 2: Short-term Secondary Prophylaxis for Early Seizures and Long-term Secondary Prophylaxis for Late Seizures

Patients who develop a seizure within the first week after the stroke, i.e., an early seizure, receive a one-week course of anticonvulsant therapy (aka short-term secondary prophylaxis). Patients subsequently remain off of therapy, unless they develop a later seizure or recurrent seizures past the first one-week period, at which point they receive anticonvulsant therapy for life, i.e., long-term secondary prophylaxis.

Strategy 3: Long-term Secondary Prophylaxis

Patients receive lifetime anticonvulsant therapy, which is started only after a post-stroke seizure, i.e., long-term secondary prophylaxis. The post-stroke seizure could occur at any time after the stroke.

Model parameters

Table 1 displays the model parameters.

Probability of Early Seizures

Although validated risk scores for early seizures exist for patients undergoing EEG monitoring,[7,8] post-stroke EEG monitoring is neither universal nor part of standard recommended practice for AIS. There also does not exist any validated EEG-based early seizure risk stratification tool for AIS. For the baseline incidence of an early seizure, we used a pooled estimate (3.3%, 95% CI 2.8–3.9%) derived from a meta-analysis.[1] We varied this baseline risk in sensitivity analyses. If the patient presented with an early seizure, we extrapolated seizure recurrence risk from the estimated cumulative risk for a late seizure given the occurrence of an early seizure.

Probability of Late Seizures

We selected a score (SeLECT) for stratified prediction of late seizure risk that was validated across four European countries (Supplemental Methods).[9] The final score can vary from 0 to 9 and can be used to ascertain 1- and 5-year cumulative risks for a late seizure. In the decision tree, we used this 5-year estimate to extrapolate the patient's cumulative lifetime probability for late seizure occurrence and recurrence (Table 1).

Anticonvulsant Efficacy

In the absence of available data estimating the efficacy of anticonvulsants in preventing a first seizure (primary prophylaxis), we extrapolated this estimation from studies that assessed efficacy of secondary prophylaxis in patients with early seizures or late seizures after AIS.[10–14] Therefore we defined anticonvulsant efficacy as the probability of prevention of both new-onset or recurrent seizures regardless of the timing of their occurrence. We computed a weighted average of anticonvulsant efficacy of 68% taken from RCTs and observational studies assessing both old and new generation anticonvulsants.[10–14] We used the efficacy value to modify the patient's estimated probability of early seizure (pES) and late seizure (pLS) while on anticonvulsant prophylaxis (e.g., pLS on anticonvulsant = pLS × (1 – anticonvulsant efficacy)).

Probability of Anticonvulsant-related ADRs

We estimated a weighted-average ADR probability of 33% using data abstracted from RCTs and an observational study.[4,10,11]

Annual Excess Mortality after AIS, Post-stroke Epilepsy Mortality, and Life Expectancy

Using data from one observational study,[15] a previous decision analysis estimated the average age-standardized annual excess death rate of AIS patients to be 8% per year.[16]

Several longitudinal studies have produced conflicting evidence concerning the association of post-stroke seizures and mortality.[17–20] Many have serious methodological limitations including selection biases with respect to the patients included vs. excluded, receipt of one treatment vs. another, or protocol adherence vs. not.[17,20] Moreover, several samples suffer from immortal time bias.[17–20] Therefore, in our main analysis we assumed that patients presented with the same age-standardized annual excess death rates after AIS regardless of seizure development (HR for post-stroke epilepsy mortality = 1);[18,19] in a secondary analysis, we assumed that patients with late seizures (i.e., post-stroke epilepsy) are more likely to die than those without seizures (HR for post-stroke epilepsy = 1.54) using data from a large nationwide cohort.[17] We used these estimates and U.S. mortality data to build life tables for each base case.[6]

QOL Utilities and QALY

We computed a QOL utility for AIS (uAIS = 0.63) that captured the average patient-reported QOL of mild, moderate, and severe long-term disability due to stroke taken from a systematic review.[21] We ascertained the late seizure utility (uLS = 0.79) as the ratio of patient-reported QOL scores between those with and without late seizure at 24 months poststroke.[4] We used patient-preference data obtained from a decision analysis on pharmaco-resistant epilepsy as an estimate of refractory seizure utility (uRS = 0.75).[22] In the absence of data describing the effect of early seizures on QOL, we selected a utility value (uES = 0.9) and explored the effects of this assumption via sensitivity analysis. Finally, we calculated an average ADR utility (uADR = 0.87) from a patient-reported outcome study that included patients with epilepsy seen at an outpatient epilepsy clinic.[23] Given that ADR may vary from mild to moderate to life-threatening and that this average estimate may not reflect utilities in other settings (e.g., intensive care unit), we manipulated uADR from 0 (death) to 1 (no effect on QOL) in sensitivity analyses.

The tree ended in 14 potential health states (Figure 1). We calculated the overall QOL utility of each health state as the product of QOL utilities for the events that it represented. For example, the overall QOL utility for a patient that had one early seizure, one late seizure, continued anticonvulsant therapy for life, and became seizure free at the expense of having ADR was calculated as: overall QOL utility = uAIS × uES × uLS × uADR. Using these utilities, we assessed QALY (QALY = overall QOL utility × age – adjusted life expectancy in years) as the outcome of our simulations.

Base Cases

We assessed four base cases that represent common clinical scenarios with respect to the probabilities of late seizures and ADR, as well as the utility assigned for ADR. Table 2 presents the parameters selected for these cases.

Case 1: Low Late Seizure Risk; Average ADR Risk and ADR Utility

A 40 year-old female with essential hypertension is admitted with a lacunar stroke and a NIHSS of 8. She has a 33% average risk of an ADR (pADR = 33%) and an average ADR utility score (uADR) of 0.87. Upon evaluation, her SeLECT score would be 1 (5-year LS risk = 2%) if she does not have an early seizure and 4 (5-year late seizure risk = 11%) if she does. Her age-adjusted life expectancy after stroke is 11.5 years.

Case 2: Low-intermediate Late Seizure Risk; High ADR Risk; Low ADR Utility

A 65 year-old male presents with AIS and a NIHSS of 9. The infarction involves the MCA territory, but there is no cortical involvement. The stroke is due to carotid artery stenosis. He has multiple comorbidities treated with polypharmacy and has a 60% risk of an ADR, which would reduce his QOL by 0.50 (uADR = 0.50). His SeLECT score would be 3 (5-year late seizure risk = 6%) if he does not develop an early seizure and 6 (5-year late seizure risk = 29%) if he does. His age-adjusted life expectancy after stroke is 9.0 years.

Case 3: High Late Seizure Risk; Average ADR Risk and ADR Utility

A 50 year-old male with essential hypertension presents with AIS and a NIHSS of 15. The stroke is cardioembolic and involves the MCA territory, but without cortical infarction. He has a 33% average ADR risk (pADR = 33%) and average ADR utility score of 0.87. His SeLECT score would be 5 (5-year late seizure risk = 18%) if he does not have an early seizure and 8 (5-year late seizure risk = 65%) if he does. His age-adjusted life expectancy after stroke is 10.8 years.

Case 4: High Late Seizure Risk; High ADR Risk; Very Low ADR Utility

An 80-year old female with atrial fibrillation and multiple comorbidities is admitted with AIS secondary to large-artery atherosclerosis and a NIHSS of 14. The infarction involves MCA territory and the cortex. She has a 80% ADR risk, which would reduce her QOL by 75% (uADR = 0.25). Her SeLECT score would be 6 (5-year late seizure risk = 29%) if she does not develop an early seizure and 9 (5-year late seizure risk = 83%) if she does. Her age-adjusted life expectancy after stroke is 5.8 years.

Model Assumptions

We made several simplifying assumptions in this model. First, because of the scarcity of data on stratified late seizure probabilities for longer follow-up periods, we assumed that the lifetime cumulative risk for late seizures was the same as the 5-year risk derived from the SeLECT score. Second, seizure risk was independent of age of stroke occurrence. Third, anticonvulsant efficacy was independent of ADR and it was the same across seizure types and timing (i.e., same efficacy for preventing occurrence and recurrence of early seizures and late seizures). Fourth, occurrence of AIS, all seizures, and ADRs exerted an average effect on QOL across their degrees of severity and duration, and that development of any of these events carried a lifelong impact on overall QOL represented by their utilities (uES, uLS, uADR, uRS).

Sensitivity Analysis

We used base cases 1 and 4 to perform sensitivity analyses as they exemplify patients with common ages for developing AIS and present low and high risks for late seizures, respectively. We performed one-way sensitivity analyses shifting the values of early seizure risk, ADR risk, anticonvulsant efficacy, early seizure utility, ADR utility, late seizure utility, and refractory seizure utility (Table 1). We also conducted two-way sensitivity analyses varying the following pairs of parameters: (1) ADR probability and ADR utility; (2) ADR probability and anticonvulsant efficacy; and (3) ADR probability and early seizure probability. We also assessed the outcomes for each base case when accounting for an increased mortality in patients with post-stroke epilepsy, as detailed above (Online Table 1).

RESULTS

Table 2 presents the results for each base case. For base case 1, who had low risk for late seizures and average ADR risk and ADR utility, strategies 2 and 3 produce equivalent outcomes and are preferred over strategy 1 with expected QALYs of 7.17 versus 6.91, respectively. For base case 2, with low-intermediate risk for late seizures but higher ADR probability and low ADR utility, strategies 2 and 3 are similar and preferred over strategy 1 with expected QALYs of 5.46, 5.43 and 3.93, respectively. For base case 3, who had high probability of late seizures, low risk of ADR, and average ADR utility, strategies 1, 2 and 3 are similar with expected QALYs of 6.35, 6.37, 6.40. For base case 4, with high late seizure and ADR probabilities and very low ADR utility, strategies 2 and 3 produce identical and are preferred over strategy 1 with expected QALYs of 2.85 and 1.40, respectively.

Sensitivity Analyses

Figures 2 to 4 and Online Figures 1 to 3 display the results of sensitivity analyses for base cases 1 and 4. In both cases, sensitivity analyses confirmed that strategies 2 and 3 accrued similar QALYs across a wide range of values. Strategy 2 yielded better efficacy with increasing ADR risk and/or decreasing ADR utility values. For strategy 1 to be favored in both cases, the probability of ES would need to be considerably above (i.e., base case 1: pES threshold ≥ 38.1%; base case 4: pES threshold ≥ 91.9%) the upper limit of the 95% confidence interval (2.8% – 3.9%) for the early seizure risk reported in a meta-analysis.[1] Finally, when accounting for an increased mortality in patients with post-stroke epilepsy (HR of death from post-stroke epilepsy = 1.54), the overall results of our model remained the same for each base case (Online Table 1).

DISCUSSION

We used a decision model to evaluate the net benefit of three anticonvulsant prophylaxis strategies after an incident acute ischemic stroke. We find that secondary anticonvulsant prophylaxis strategies always dominated the primary prophylaxis approach under all evaluated scenarios. Under most scenarios, the two secondary prophylaxis strategies yielded comparable outcomes on average; however, as the risk of adverse events increases or patient utilities for the resulting state decrease, short-term secondary prophylaxis becomes preferable to secondary prophylaxis continued indefinitely. Accordingly, physicians should consider individual patient risk for and preferences related to anticonvulsant treatment side effects when choosing an secondary prophylaxis strategy.

One important finding is that primary prophylaxis was persistently dominated, i.e., yielded inferior outcomes, compared with secondary prophylaxis. In fact, only when we created clinically implausible scenarios in which patients had an extremely high early seizure risk but very low ADR risk, did primary prophylaxis strategy yield outcomes comparable to other strategies. Our finding is consistent with and reaffirms current recommendations against primary prophylaxis for post-stroke seizures.[24,25] Our finding also suggests a need for clear documentation of indications for initiating anticonvulsant therapy, particularly when initiated in the hospital.

Contrary to current guidelines, we find favorable outcomes associated with early secondary anticonvulsant prophylaxis among AIS patients, i.e., therapy started after a seizure occurring within the first seven days after the stroke.[24,25] Proponents of early secondary prophylaxis argue that untreated seizures could result in preventable neuronal injury,[25,26] and that the potential benefits outweigh the potential harms when using newer anticonvulsants with more favorable safety profiles than older drugs have.[27]

All of the strategies assume continued monitoring of patients with thoughtful coordination of medical therapy across settings and physicians. The two secondary prophylaxis strategies require continued monitoring for seizures and adverse drug reactions, with potential stoppage or re-initiation of therapy, whereas the operationally simplest strategy of initiating therapy after all strokes was least optimal. In practice, this continued coordination and monitoring could be challenging as patients change doctors, receive care from many settings including hospitals and clinics, and change health insurance plans (which itself could necessitate changes in doctors). Indeed, there have been persistent concerns about patients receiving prescriptions that future physicians perpetuate indefinitely, with the resulting polypharmacy creating drug-specific risks, drug-interaction risks, and adding to the financial burden associated with prescription drugs.[28–31]

Given that the AIS population is predominantly older adults and vulnerable to ADRs,[32] prolonged secondary prophylaxis poses notable risks. For example AIS patients often concomitantly use antithrombotic medications, and a fall can be life-threatening or lead to permanent disability. Finally, our decision tree provides a framework for physicians to weigh the likely tradeoffs associated with the three levels of seizure prophylaxis. By means of adjustments in estimated average probabilities, utilities and life expectancy, the tree can be adapted to different local realities and yield results based on individual-level patient data.

Limitations

This study has several limitations. First, we estimated model parameters only from published data. We attempted to account for uncertainty via sensitivity analyses, however some derived estimates could be biased or subject to confounding. Little is known, for example, about anticonvulsant efficacy in preventing the occurrence of a first early seizure or development of a first late seizure after AIS. Therefore we selected an estimate derived from studies that assessed efficacy in preventing late seizure recurrence, but without direct comparisons of anticonvulsants against no intervention.[10,11,13,14] The estimated lifetime ADR risk is also limited because studies assessed safety outcomes only in patients taking anticonvulsants and for relatively short periods (≤ 24 months).[4,11,14] Consequentially our estimate may not be accurate because some ADRs (e.g., fall, dizziness) could be present among those not taking anticonvulsants.

Additionally, our utility estimations may not capture all aspects of patient preference and interpatient variation is likely. We obtained ADR utility from one study conducted in an outpatient setting that compared single-visit, patient-reported QOL among patients with epilepsy. This estimate might not generalize to other settings, those with longer periods of medication use, or those with post-stroke seizures. Similarly, we derived the refractory seizure utility from a single study that obtained preference-based QOL values from patients with pharmacoresistant temporal lobe epilepsy, which may not generalize to post-stroke epilepsy patients. We also did not account for EEG abnormalities in our analysis..[3334] Continuous inpatient EEG monitoring is increasing in use[35] with accumulating evidence that some EEG patterns are associated with increased seizure and epilepsy risk.[7,8] As the evidence base improves, we may need to update our model to include EEG findings.

Finally, for model simplicity we did not address: 1) how stroke treatment type (i.e., no intervention, intravenous thrombolysis, endovascular treatment) factors into seizure risk; 2) risk for stroke recurrence and how a new event changes the likelihood of developing further seizures; 3) determinants of anticonvulsant adherence, such as comorbidities, socioeconomic characteristics, or co-medications; 4) the effect of age on post-stroke seizure risk after AIS; and 5) any risk differences by sex because of a lack of data on sex as a biological determinant of seizure or complication risk. We also assumed that anticonvulsant efficacy and ADR risk were independent, which is not accurate in a real-world setting. As higher-quality epidemiologic data is obtained, future improvements to our model could add parameters that influence subsequent seizure risk and mortality attributable to stroke or seizures, such as specific seizure type, adherence to anticonvulsant therapy, choice of anticonvulsant therapy, or potential interactions between some anticonvulsants and vascular prophylaxis. And to evaluate the validity of this model's findings, our future work will use the experience of Medicare beneficiaries nationally to assess the benefits and risks of seizure prophylaxis using real-world data.

In sum, there currently are no trial data with which to guide anticonvulsant therapy after an incident ischemic stroke. In the absence of a rigorous evidence base, our decision analysis highlights tradeoffs associated between post-stroke seizures and adverse effects resulting from seizure prophylaxis. In all of the clinical scenarios tested, starting prophylaxis only after a post-stroke seizure (i.e., secondary prophylaxis) dominates primary prophylaxis. Moreover, in several scenarios, maintaining prophylaxis for a finite time period also yields better patient outcomes than continuing treatment indefinitely. These findings strongly suggest the need to monitor patients closely after a stroke, ensure adequate coordination of medication therapy, and consider individual patient and family preferences with respect to utilities associated with future seizure- and treatment-related risks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NON-STANDARD ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
AIS	acute ischemic stroke
MCA	middle cerebral artery
NIHSS	National Institute of Health Stroke Scale
QALY	quality-adjust life year
QOL	quality of life

REFERENCES

1. Wang JZ, Vyas MV, Saposnik G, Burneo JG. Incidence and management of seizures after ischemic stroke. Neurology. 2017;89:1220–1228. [PubMed: 28835405]
2. Merkler AE, Gialdini G, Lerario MP, et al.Population-Based Assessment of the Long-Term Risk of Seizures in Survivors of Stroke. Stroke. United States; 2018;49:1319–1324.

3. Huang C-W, Saposnik G, Fang J, Steven DA, Burneo JG. Influence of seizures on stroke outcomes: a large multicenter study. Neurology. United States; 2014;82:768–776.

4. Winter Y, Daneshkhah N, Galland N, Kotulla I, Krüger A, Groppa S. Health-related quality of life in patients with poststroke epilepsy. Epilepsy Behav. 2018;80:303–306. [PubMed: 29429905]

5. US Department of Health and Human Services. 42 CFR Part 11: Clinical Trials Registration and Results Information Submission [online]. Fed. Regist2016. Accessed at: https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission.

6. Salkind N, Anderson RN. National Vital Statistics Reports. Encycl Hum Dev. 2013;68.

7. Struck AF, Ustun B, Ruiz AR, et al.Association of an Electroencephalography-Based Risk Score With Seizure Probability in Hospitalized Patients. JAMA Neurol. 2017;74:1419. [PubMed: 29052706]

8. Struck AF, Tabaeizadeh M, Schmitt SE, et al.Assessment of the Validity of the 2HELPS2B Score for Inpatient Seizure Risk Prediction. JAMA Neurol. 2020;77:500. [PubMed: 31930362]

9. Galovic M, Dohler N, Erdelyi-Canavese B, et al.Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. Lancet Neurol. England; 2018;17:143–152.

10. 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;34:282–289. [PubMed: 23128439]

11. Gilad R, Sadeh M, Rapoport A, Dabby R, Boaz M, Lampl Y. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol. 2007;30:189–195. [PubMed: 17762314]

12. Gilad R, Lampl Y, Eschel Y, Sadeh M. Antiepileptic Treatment in Patients with Early Postischemic Stroke Seizures: A Retrospective Study. Cerebrovasc Dis. 2001;12:39–43. [PubMed: 11435678]

13. Rowan AJ, Ramsay RE, Collins JF, et al.New onset geriatric epilepsy: A randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology. 2005;64:1868–1873. [PubMed: 15955935]

14. Kim HJ, Park KD, Choi K-G, Lee HW. Clinical predictors of seizure recurrence after the first post-ischemic stroke seizure. BMC Neurol. England; 2016;16:212.

15. Lai SM, Alter M, Friday G, Sobel E. Prognosis for Survival After an Initial Stroke. Stroke. 1995;26:2011–2015. [PubMed: 7482640]

16. Eckman MH, Rosand J, Knudsen KA, Singer DE, Greenberg SM. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke. 2003;34:1710–1716. [PubMed: 12805495]

17. Zelano J, Redfors P, Åsberg S, Kumlien E. Association between poststroke epilepsy and death: A nationwide cohort study. Eur Stroke J [online serial]. 2016;1:272–278. Accessed at: http://journals.sagepub.com/doi/10.1177/2396987316669000.

18. Merlino G, Gigli GL, Bax F, Serafini A, Corazza E, Valente M. Seizures Do Not Affect Disability and Mortality Outcomes of Stroke: A Population-Based Study. J Clin Med. 2019;8:2006.

19. van Tuijl JH, van Raak EPM, van Oostenbrugge RJ, Aldenkamp AP, Rouhl RPW. The occurrence of seizures after ischemic stroke does not influence long-term mortality; a 26-year follow-up study. J Neurol. Springer Berlin Heidelberg; 2018;265:1780–1788.

20. Arntz RM, Rutten-Jacobs LCA, Maaijwee NAM, et al.Poststroke Epilepsy Is Associated With a High Mortality After a Stroke at Young Age. Stroke [online serial]. 2015;46:2309–2311. Accessed at: https://www.ahajournals.org/doi/10.1161/STROKEAHA.115.010115.

21. Ward S, Lloyd Jones M, Pandor A, et al.A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess (Rockv). 2007;11.

22. Choi H, Sell RL, Lenert L, et al.Epilepsy Surgery for Pharmacoresistant. Jama. 2008;300:2497–2505. [PubMed: 19050193]

23. Moura LMVR, Magliocco B, Ney JP, Cheng EM, Esper GJ, Hoch DB. Implementation of quality measures and patient-reported outcomes in an epilepsy clinic. Neurology. 2019;93:E2032–E2041. [PubMed: 31666351]

24. Powers WJ, Rabinstein AA, Ackerson T, et al.2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke2018.
25. 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;2:103–115. [PubMed: 31008306]
26. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological Mechanisms of Brain Damage from Status Epilepticus. Epilepsia. 1993;34:S37–S53. [PubMed: 8385002]
27. LaRoche SM, Helmers SL. The New Antiepileptic Drugs. JAMA. 2004;291:605. [PubMed: 14762040]
28. Kojima G, Bell C, Tamura B, et al.Reducing Cost by Reducing Polypharmacy: The Polypharmacy Outcomes Project. J Am Med Dir Assoc [online serial]2012;13:818.e11–818.e15. Accessed at: https://linkinghub.elsevier.com/retrieve/pii/S1525861012002423.
29. Johnell K, Klarin I. The Relationship between Number of Drugs and Potential Drug-Drug Interactions in the Elderly. Drug Saf [online serial]. 2007;30:911–918. Accessed at: http://link.springer.com/10.2165/00002018-200730100-00009.
30. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999–2012. JAMA [online serial]. 2015;314:1818. Accessed at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2015.13766.
31. Montero-Odasso M, Sarquis-Adamson Y, Song HY, Bray NW, Pieruccini-Faria F, Speechley M. Polypharmacy, Gait Performance, and Falls in Community-Dwelling Older Adults. Results from the Gait and Brain Study. J Am Geriatr Soc [online serial]. 2019;67:1182–1188. Accessed at: http://doi.wiley.com/10.1111/jgs.15774.
32. Perucca E, Berlowitz D, Birnbaum A, et al.Pharmacological and clinical aspects of antiepileptic drug use in the elderly. Epilepsy Res. 2006;68:49–63.
33. Fisher RS, Van Emde Boas W, Blume W, et al.Response: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) [4]. Epilepsia. 2005;46:1701–1702.
34. Chong DJ, Hirsch LJ. Which EEG Patterns Warrant Treatment in the Critically Ill? Reviewing the Evidence for Treatment of Periodic Epileptiform Discharges and Related Patterns. J Clin Neurophysiol. 2005;22:79–91. [PubMed: 15805807]
35. Ney JP, van der Goes DN, Nuwer MR, Nelson L, Eccher MA. Continuous and routine EEG in intensive care: Utilization and outcomes, United States 2005–2009. Neurology. 2013;81:2002–2008. [PubMed: 24186910]
36. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: A decision analysis. Arch Neurol. 2011;68:573–579. [PubMed: 21220650]

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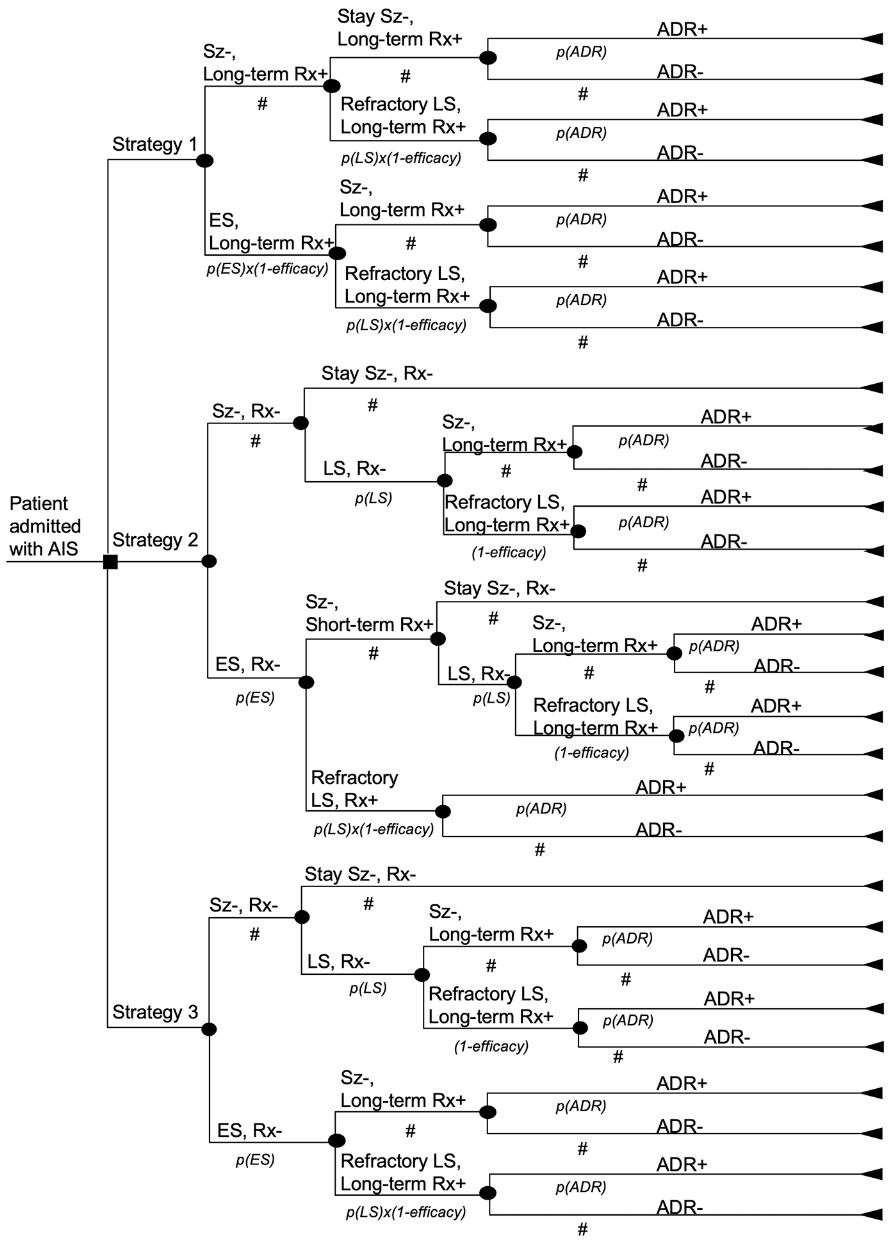

Figure 1. Decision Tree

Abbreviations: AIS, acute ischemic stroke; Sz−, seizure free; ES, early seizure; LS, late seizure; Rx+, anticonvulsant prophylaxis; Rx−, no anticonvulsant prophylaxis; ADR+, anticonvulsant-related adverse drug reaction; ADR−, no anticonvulsant-related adverse drug reaction; p, probability.

Strategy 1: Long-term primary prophylaxis;

Strategy 2: Short-term secondary prophylaxis after early seizure and long-term prophylaxis after late seizure;

Strategy 3: Long-term secondary prophylaxis after early or late seizures.

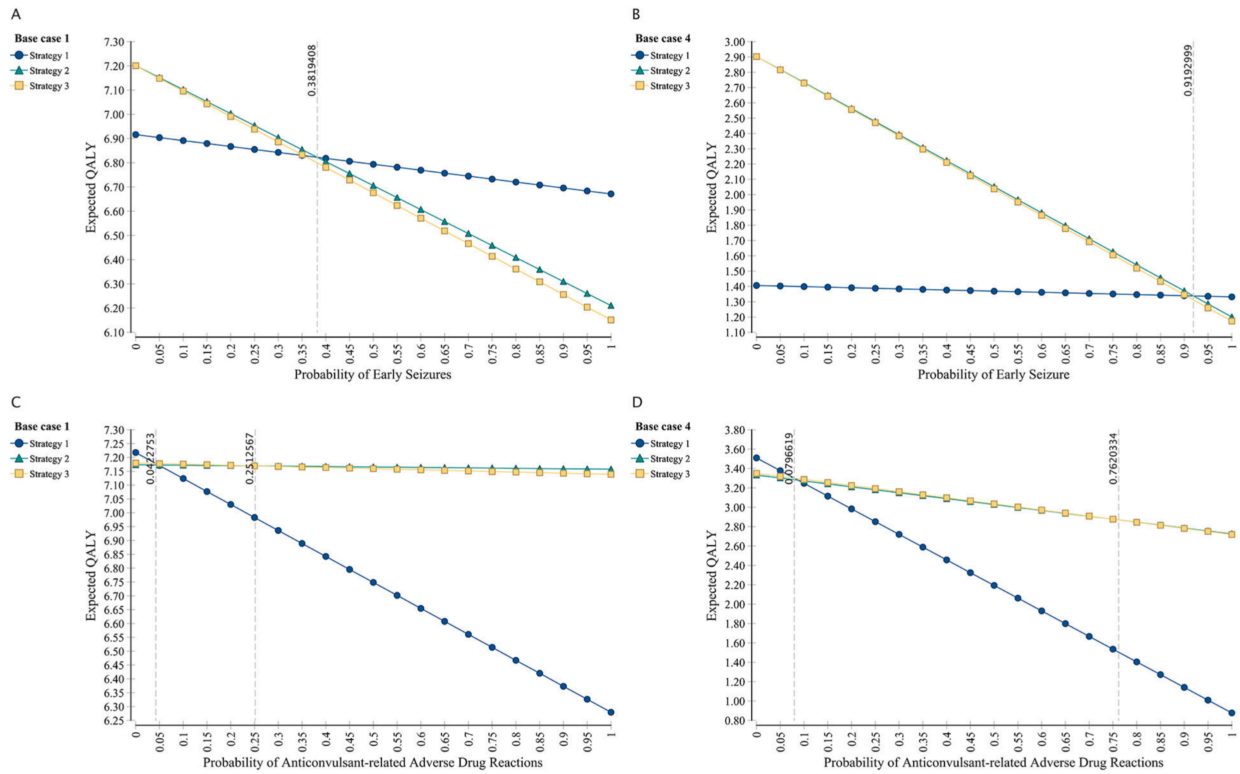

Figure 2. One-way sensitivity analyses

Abbreviation: QALY, quality-adjusted life expectancy;

Strategy 1: Long-term primary prophylaxis;

Strategy 2: Short-term secondary prophylaxis after early seizure and long-term prophylaxis after late seizure;

Strategy 3: Long-term secondary prophylaxis after early or late seizures.

One-way sensitivity analyses performed on base cases 1 and 4 to assess the effects of varying values for early seizure probability (A & B) and ADR probability (C & D).

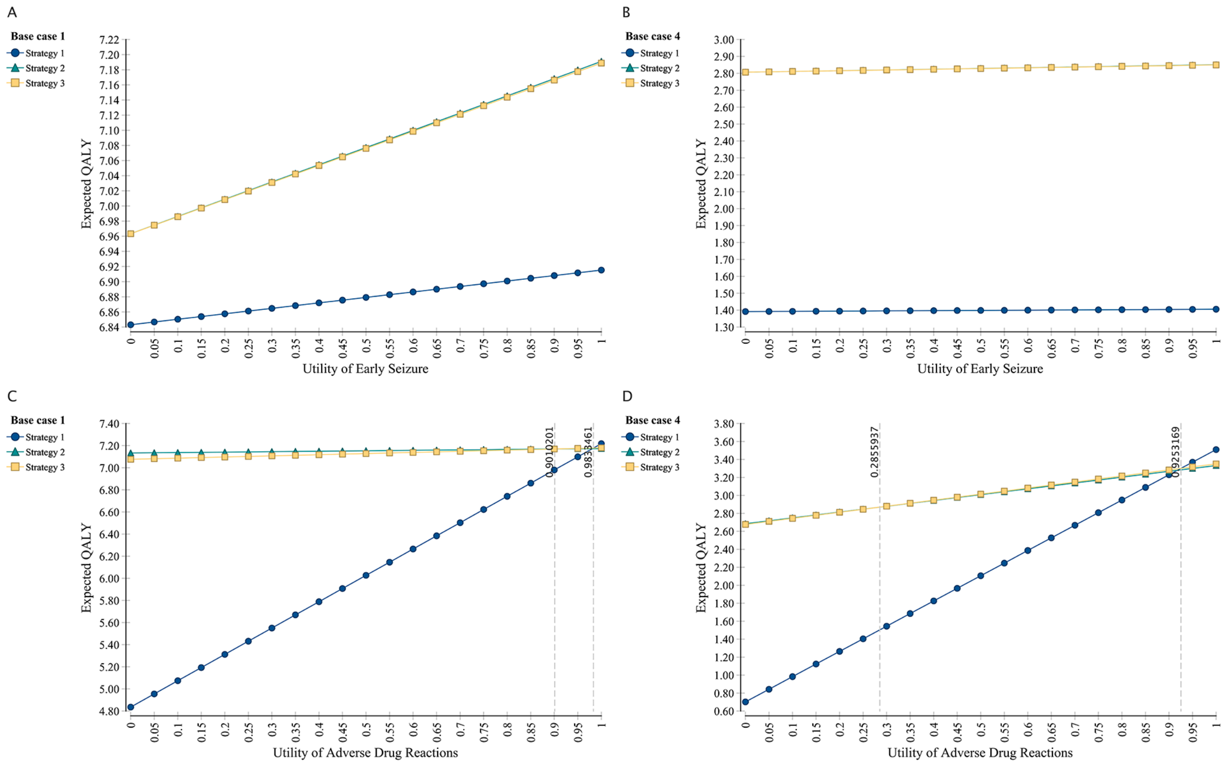

Figure 3. One-way sensitivity analyses

Abbreviations: QALY, quality-adjusted life expectancy;

Strategy 1: Long-term primary prophylaxis;

Strategy 2: Short-term secondary prophylaxis after early seizure and long-term prophylaxis after late seizure;

Strategy 3: Long-term secondary prophylaxis after early or late seizures.

One-way sensitivity analyses performed on base cases 1 and 4 to assess the effects of varying values for early seizure utility (A & B) and ADR utility (C & D).

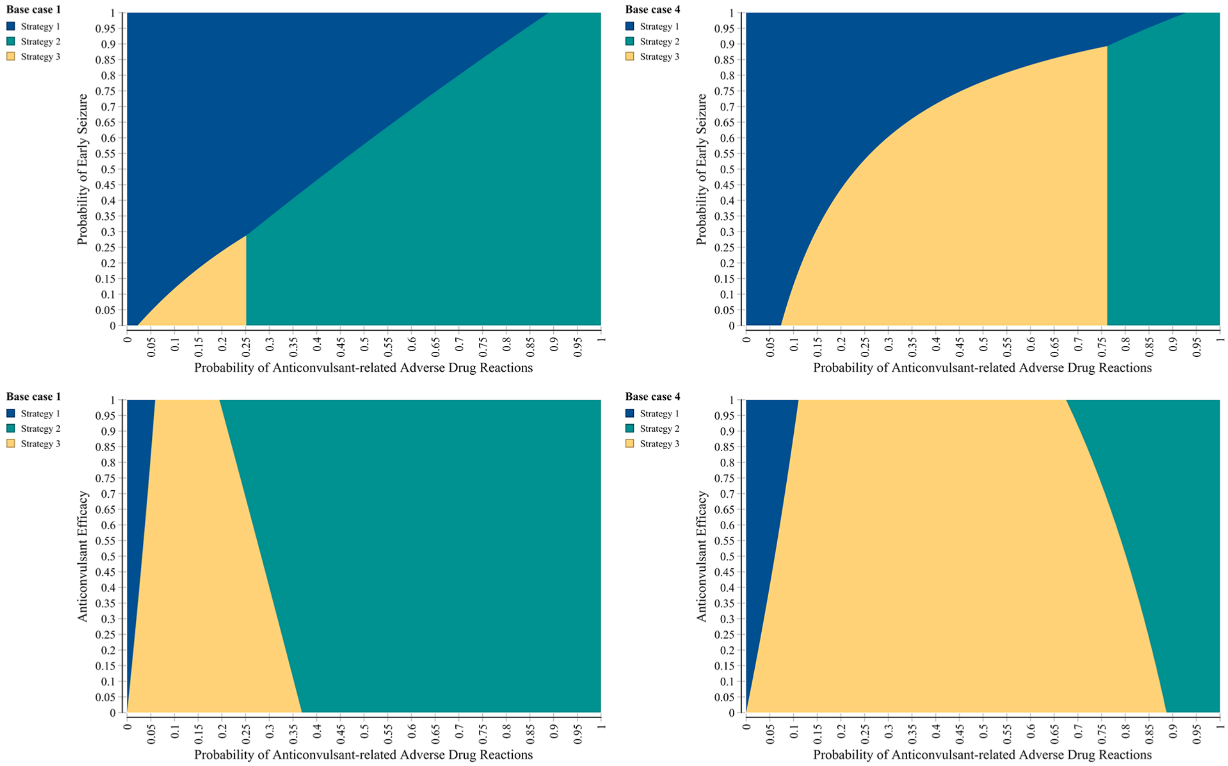

Figure 4. Two-way sensitivity analyses

Abbreviations: QALY, quality-adjusted life expectancy;

Strategy 1: Long-term primary prophylaxis;

Strategy 2: Short-term secondary prophylaxis after early seizure and long-term prophylaxis after late seizure;

Strategy 3: Long-term secondary prophylaxis after early or late seizures.

Two-way sensitivity analyses performed on base cases 1 and 4 to assess the effects of varying early seizure probability and ADR probability (A & B); ADR probability and anticonvulsant efficacy (C & D).

Table 1.

Model parameters

Characteristic	Source	Estimate (95% CI)	Sensitivity Analysis
Probabilities			
Early seizure	Wang et al, 2017[1]	3.3% (2.8–3.9%)	0.0 – 100.0
Late seizure, SeLECT* = 0	Galovic et al, 2018[9]	1.3% (0.7–1.8%)	Base case 1: 2.0 or 11.0 Base case 4: 29.0 or 83.0
Late seizure, SeLECT* = 1		2.0% (1.0–3.0%)	
Late seizure, SeLECT* = 2		4.0% (3.0–5.0%)	
Late seizure, SeLECT* = 3		6.0% (5.0–8.0%)	
Late seizure, SeLECT* = 4		11.0% (9.0–13.0%)	
Late seizure, SeLECT* = 5		18.0% (15.0–21.0%)	
Late seizure, SeLECT* = 6		29.0% (23.0–35.0%)	
Late seizure, SeLECT* = 7		45.0% (34.0–54.0%)	
Late seizure, SeLECT* = 8		65.0% (48.0–76.0%)	
Late seizure, SeLECT* = 9		83.0% (62.0–93.0%)	
Anticonvulsant efficacy†	Kim et al, 2016[14] Consoli et al, 2012[10] Gilad et al, 2007[11] Rowan et al, 2005[13] Gilad et al, 2001[12]	68.0%	30.0 – 100.0
Anticonvulsant-related adverse drug reaction	Winter et al, 2018[4] Consoli et al, 2012[10] Gilad et al, 2007[11]	33.0%	0.0 – 100.0
Annual excess death rate due to stroke	Echman et al, 2003[16] Lai et al, 1995[15]	8.0%	Not varied
Hazard ratio of death due to post-stroke epilepsy	Merlino, 2019[18] Van Tuijl, 2018[19] Zelano, 2016[17]	1.0	1.54
QOL utilities			
Acute ischemic stroke	Westover et al, 2011[36] Ward et al, 2007[21]	0.63	Not varied
Early seizure	Authors' choice	0.90	0.0 – 1.0
Late seizure	Winter et al, 2018[4]	0.79	0.0 – 1.0
Refractory seizure	Choi et al, 2011[22]	0.75	0.0 – 1.0
Anticonvulsant-related adverse drug reaction	Moura et al, 2019[23]	0.87	0.0 – 1.0

Abbreviations: QOL indicates quality of life.

*SeLECT score values are calculated by adding points for the following clinical characteristics: National Institute of Health Stroke Scale (NIHSS ≤ 3 = 0 points; NIHSS 4–10 = 1 point; NIHSS ≥ 11 = 2 points), large-artery atherosclerosis etiology (no = 0 points; yes = 1 point), early seizure development (no = 0 points; yes = 3 points), cortical involvement (no = 0 points; yes = 2 points), territory of MCA involvement (no = 0 points; yes = 1 point). The final score value estimates 5-year cumulative risk for late seizures.

†Anticonvulsant efficacy defined as probability of becoming seizure free while on anticonvulsant.

Table 2.

Base cases and outcomes

Base case	Age (life expectancy), y	Probability of LS, %		Probability of ADR, %	ADR utility	Tree outcome, QALY			Preferred decision
		No early seizure	Early seizure			Strategy 1*	Strategy 2†	Strategy 3‡	
Case 1	40 (11.5)	2	11	33	0.87	6.91	7.17	7.17	Strategy 2/3
Case 2	65 (9.0)	6	29	60	0.50	3.93	5.46	5.43	Strategy 2
Case 3	50 (10.8)	18	65	33	0.87	6.35	6.37	6.40	Strategy 3
Case 4	80 (5.8)	29	83	80	0.25	1.40	2.85	2.85	Strategy 2/3

Abbreviations: y indicates years; ADR, anticonvulsant-related adverse drug reaction; QALY, quality-adjusted life years.

*Strategy 1: Long-term primary prophylaxis;

†Strategy 2: Short-term anticonvulsant secondary prophylaxis after early seizure and long-term prophylaxis after late seizure;

‡Strategy 3: Long-term anticonvulsant secondary prophylaxis after early or late seizures.