



# One Size Does Not Fit All: Risk Stratification in Seizure Prophylaxis

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## Keywords

Intracerebral hemorrhage, seizures, anti-seizure medication, prophylaxis, decision analysis, sensitivity analysis

Jones FJS, Sanches PR, Smith JR, et al. Seizure Prophylaxis After Spontaneous Intracerebral Hemorrhage. *JAMA Neurol.* 2021; 78(9):1128-1136. doi:10.1001/jamaneurol.2021.2249

**Importance:** Limited evidence is available concerning optimal seizure prophylaxis after spontaneous intracerebral hemorrhage (sICH). **Objective:** To evaluate which of 4 seizure prophylaxis strategies provides the greatest net benefit for patients with sICH. **Design, Setting and Participants:** This decision analysis used models to simulate the following 4 common scenarios: (1) a 60-year-old man with low risk of early ( $\leq 7$  days after stroke) (10%) and late (3.6% or 9.8%) seizures and average risk of short- (9%) and long-term (30%) adverse drug reaction (ADR), (2) an 80-year-old woman with low risk of early (10%) and late (3.6% or 9.8%) seizures and high short- (24%) and long-term (80%) ADR risks, (3) a 55-year-old man with high risk of early (19%) and late (34.8% or 46.2%) seizures and low short- (9%) and long-term (30%) ADR risks, and (4) a 45-year-old woman with high risk of early (19%) and late (34.8% or 46.2%) seizures and high short- (18%) and long-term (60%) ADR risks. **Interventions:** The following 4 anti-seizure drug strategies were included: (1) conservative, consisting of short-term (7-day) secondary early-seizure prophylaxis with long-term therapy after late seizure; (2) moderate, consisting of long-term secondary early-seizure prophylaxis or late-seizure therapy; (3) aggressive, consisting of long-term primary prophylaxis; and (4) risk guided, consisting of short-term secondary early-seizure prophylaxis among low-risk patients (2HELPS2B score, 0), short-term primary prophylaxis among patients at higher risk (2HELPS2B score,  $\geq 1$ ), and long-term secondary therapy for late seizure. **Main Outcomes and Measures:** Quality-adjusted life years (QALYs). **Results:** For scenario 1, the risk-guided strategy (8.13 QALYs) was preferred over the conservative (8.08 QALYs), moderate (8.07 QALYs) and aggressive (7.88 QALYs) strategies. For scenario 2, the conservative strategy (2.18 QALYs) was preferred over the risk-guided (2.17 QALYs), moderate (2.09 QALYs) and aggressive (1.15 QALYs) strategies. For scenario 3, the aggressive strategy (9.21 QALYs) was preferred over the risk-guided (8.98 QALYs), moderate (8.93 QALYs) and conservative (8.77 QALYs) strategies. For scenario 4, the risk-guided strategy (11.53 QALYs) was preferred over the conservative (11.23 QALYs), moderate (10.93 QALYs) and aggressive (8.08 QALYs) strategies. Sensitivity analyses suggested that short-term strategies (conservative and risk-guided) are preferred under most scenarios, and the risk-guided strategy performs comparably to or better than alternative strategies in most settings. **Conclusions and Relevance:** This decision analytical model suggests that short-term (7-day) prophylaxis dominates longer-term therapy after sICH. Use of the 2HELPS2B score to guide clinical decisions for initiation of short-term primary vs secondary early-seizure prophylaxis should be considered for all patients after sICH.

## Commentary

We have all seen it before, sitting in the clinic reviewing a patient's medication list. Why are you on this anti-seizure medication (ASM)? The answer is often "I was put on it in the hospital years ago and it was never stopped". Many doctors do not feel confident to stop an ASM. To change a culture of unnecessary ASM use, we need evidence guidance for ourselves and our colleagues in the wider medical community. Jones's study cleverly uses decision analysis of already existing data, demonstrated in a practical case-based way, to answer the

question of ASM prophylaxis after spontaneous intracranial haemorrhage (sICH).

Current guidelines recommend treatment with ASM for electrographic or clinical seizures post sICH (but no guidance on duration of treatment) and do not recommend primary prophylaxis.<sup>1</sup> The effect of seizure prophylaxis on outcome is unclear.<sup>2</sup> However, use of ASM for seizure prophylaxis in this setting remains common.<sup>(3)</sup>

Jones asked which seizure prophylaxis strategy provided the best outcomes for patients, as measured by quality-adjusted life-years (QALYs), after spontaneous intracranial





haemorrhage in patients over 18 years without prior history of stroke or epilepsy.

To enhance understanding of the article, it is useful to review some definitions. Primary prophylaxis was treatment on hospital admission with an ASM. Early secondary prophylaxis involves treatment with an ASM after a seizure occurring in the first 7 days. Late secondary prophylaxis involves use of an ASM when a seizure happens after 7 days. Short-term treatment is a 7-day duration, while long-term treatment is indefinite. For example, short-term early secondary prophylaxis would be a 7-days treatment with an ASM for a seizure that occurred 2 days after admission.

A decision analysis model used existing data from peer-reviewed published studies. This included data on average risks of early or late seizures after sICH, ASM-related adverse drug reactions (ADR) and expected ASM efficacy.<sup>(4,5)</sup>

Four strategies of seizure prophylaxis on diagnosis of a sICH were compared. The risk-guided strategy uses the 2HELPS2B score. This score can help estimate early seizure risk during hospitalization in medically or neurologically ill patients, mainly using continuous EEG (cEEG) data. Five cEEG data points and one clinical datapoint calculate the score, which assigns risk from 5% (0 points) to 95% (7 points). Essentially, epileptiform features on EEG or history of prior or recent seizures gives a score of .4

1. Conservative
  - a Monitor clinically for seizures, if early seizure occurs—short-term secondary prophylaxis. If late seizure occurs, then long-term prophylaxis.
2. Moderate
  - a Monitor clinically for seizures, if early seizure occurs—long-term secondary prophylaxis. If late seizure occurs, then long-term prophylaxis
3. Aggressive
  - a Long-term prophylaxis on admission regardless of the occurrence of seizures
4. Risk-guided using 2HELPS2B score
  - a cEEG screening, low risk (score 0)—conservative
  - b cEEG screening, medium or high risk (score  $\geq 1$ )—short-term primary prophylaxis. If late seizure, then long-term prophylaxis.

Decision modelling or decision tree analysis uses existing evidence to look at the effects of alternate strategies; the decision tree allows a visual representation of the effect of risk events on the outcome, as they occur over a fixed period of time (in this case, from hospital admission for sICH until the remaining expected lifetime).

The outcomes were measured in accrued quality-adjusted life years (QALYs). A QALY is a health measure by years of life in perfect health. A QALY score is obtained by the product of a person's age-adjusted life expectancy and a quality of life (QOL) utility score, a number between 0 (death) and 1 (perfect health), specific to an underlying health condition. QOL utility scores were based on data from prior studies of subjective patient-estimated QOL after sICH, as well as those associated

with early, late or refractory seizures, and short- or long-term ASM ADR.

For example, the QOL utility score is estimated to be .75 for a patient with refractory epilepsy, and .6 for sICH—for a patient with refractory epilepsy after sICH, it would be .45 ( $.75 \times .6$ ). If they had a 20-year life expectancy, their QALY would be  $20 \times .45 = 9$ .

Age-adjusted life expectancy in this study was derived from a life table generated from US mortality ratios and the standardized mortality ratio (SMR) of sICH from a European population-based study. A life table shows the probability that a person will die before their next birthday at each year of age.

Four scenarios typical for sICH are presented, although theoretically any combination of variables could be used.

Case 1 was a 60-year-old man with a deep hypertensive sICH, with a low seizure risk and average risk of ADR with a life expectancy of 13.8 years. The best prophylaxis strategy was risk guided, with 8.13 QALYs.

Case 2 was an 80-year-old woman with a subcortical sICH due to amyloid, with a low seizure risk, and high risk of ADR, and a life expectancy of 3.7 years. The best prophylaxis strategy was conservative with 2.18 QALYs.

Case 3 was a 55-year-old man with lobar sICH due to cocaine use, with a high seizure risk and average risk of ADR, with a life expectancy of 17 years. The best prophylaxis strategy was aggressive with 9.21 QALYs.

Case 4 was a 45-year-old woman with lobar sICH, with a high seizure risk and high risk of ADR, with a life expectancy of 24.7 years. The best prophylaxis strategy was risk guided, with 11.53 QALYs.

The study, for simplicity, made assumptions on long-term seizure risks, ASM compliance and constant QOL utilities throughout the lifetime. There is also bias from using published literature data, and the qualitative nature of QOL utility theory. In addition, decision tree analysis implies no recurrent events to be accurate. However, despite these assumptions, outcomes were consistent on testing with sensitivity analysis. The outcomes in QALYs are estimates based on probabilities, but give a more real-world insight into the effect of a strategy on the patient's overall health.

The study model allows the use of sensitivity analysis, a widely accepted but underutilized method to test a study hypothesis and outcome, and provide complementary insights. Different ranges of parameter values (i.e. increasing ADR risk or early seizure risk) are used to see how they affect the outcome. If they remain similar across the range, then the model is more likely to be credible.

The sensitivity analysis found that the risk-guided strategy performed better in most ranges. The aggressive strategy is favoured if late seizure risk was high and ADR risk low. The conservative strategy was favoured if ADR risk was high and life expectancy was short.

This study, while making some assumptions, elegantly shows how existing quality data can be modelled to answer everyday questions in epileptology.

Long-term ASM failed to provide better outcomes in most cases, and early discontinuation of ASM started before or after




early seizure (for early prophylaxis) is to be encouraged, unless late seizure risk is high and risk of ADR low.

The risk-guided strategy suggests short-term primary prophylaxis is beneficial if cEEG is abnormal ( $2\text{HELPS2B} \geq 1$ ). Whether this prevents early seizures or late-onset seizures is unclear, but emerging evidence has shown treatment on detection of EEG epileptiform activity results in better outcomes.<sup>(6)</sup> Availability of cEEG limits the use of the risk-guided strategy. In this case, the authors suggest a more conservative strategy.

Higher mortality risks and reduced availability of newer ASM in some countries limit generalisability of the model. However, the decision model could be adapted for alternate risk scenarios.

Careful consideration to appropriate ASM prophylaxis for the individual patient after sICH should be given both during initial admission and on review in later clinics.

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