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Seizure Prophylaxis After Spontaneous Intracerebral Hemorrhage

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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 (≤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 antiseizure 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, ≥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.

Multimedia

Supplemental content

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Acute symptomatic seizures (early seizures, ≤7 days after stroke) are a common complication of spontaneous intracerebral hemorrhage (sICH). The estimated risk for early seizure among adult patients ranges from 10% to 19%.[1] Early seizures are associated with worse neurological outcomes, including unprovoked seizures (late seizures, >7 days after stroke) and epilepsy.[2-4]

In the case of seizure prophylaxis after sICH, guideline recommendations and current clinical practice are misaligned, perhaps in part because of a lack of high-quality clinical trials.[5] Although potential safety concerns prompted recommendations against use of antiseizure drugs for primary prophylaxis,[5] the literature indicates approximately 40% of US patients with sICH receive prophylactic levetiracetam before seizure development.[6,7] Prophylaxis duration may also vary substantially, ranging from short- to long-term strategies.[7-9] Because seizure risk is a key determinant of which patient groups might benefit most from different prophylaxis strategies, validated tools for predicting early (eg, 2HELPS2B score) and late (eg, CAVE score [cortical involvement, age <65 years, sICH volume >10 mL, and early seizures]) seizure risks could aid physicians in treatment decisions.[4,10,11] However, no clinical trials or prospective studies have evaluated the net benefit of various strategies after sICH.

Therefore, we used a simulation model and decision analysis to incorporate current knowledge and evaluate the tradeoffs associated with 4 treatment strategies based on the type of therapy (primary vs secondary prophylaxis), timing of event (early vs late seizures), and duration of therapy (1 week [short-term] vs indefinite [long-term] therapy). The strategies included (1) conservative short-term secondary prophylaxis after early seizures and long-term therapy after late seizures; (2) moderate long-term secondary prophylaxis after early seizure or long-term secondary therapy after late seizure; (3) aggressive long-term primary prophylaxis; or (4) risk-guided short-term secondary prophylaxis after early seizure among low-risk patients (2HELPS2B risk score), short-term primary prophylaxis among higher-risk patients, and long-term secondary therapy after late seizure.[11] We aimed to answer which option is associated with the greatest net benefit, measured as expected quality-adjusted life-years (QALYs).

Key Points

Question Which of 4 antiseizure drug prophylaxis strategies provides the most quality-adjusted life-years on average for patients with an incident spontaneous intracerebral hemorrhage (sICH)?

Findings In this decision analysis simulating 4 common clinical scenarios, short-term (7-day) early-seizure prophylaxis strategies dominated long-term therapy under most clinical scenarios. A risk-guided strategy using a risk stratification tool (2HELPS2B) to identify patients likely to benefit from short-term primary vs secondary prophylaxis performed comparably or better than alternative strategies in most settings.

Meaning This decision analysis underscores the importance of early discontinuation of antiseizure drug therapy initiated before or after early seizures; use of the 2HELPS2B score to guide the clinical decision on initiation of short-term primary vs secondary early-seizure prophylaxis should be considered for all patients after sICH, assuming timely availability of electroencephalography.

Methods

In this decision analysis study, we built a decision tree model (eFigure 1 in the Supplement) using TreeAge Pro Healthcare (TreeAge Software LLC). We modeled seizure prophylaxis management in adult patients 18 years or older, without a history of epilepsy or stroke, who present with an incident sICH. The tree's timeline follows each patient's admission to the hospital due to newly diagnosed sICH through the patient's remaining expected lifetime, as estimated by age-adjusted life expectancy after sICH.[12] Based on published data, the tree includes average risks and quality-of-life (QOL) utilities for the occurrence of early seizure, late seizure, refractory seizure, antiseizure drug–related adverse drug reaction (ADR), antiseizure drug efficacy for preventing seizures, and the 2HELPS2B's test characteristics for predicting early-seizure development. The tree's outcome is the number of QALYs, a product of the QOL utility scores and life expectancy. The preferred treatment strategy is the one yielding the most QALYs. We used 4 common clinical scenarios to evaluate the 4 prophylaxis strategies: (1) a patient with a low risk of late seizure and average ADR risk and utility; (2) a patient with a low risk of late seizure, high ADR risk, and low ADR utility; (3) a patient with a high risk of late seizure and average ADR risk and utility; and (4) a patient with a high risk of late seizure, high ADR risk, and low ADR utility. All data analyzed in this study are included in this report and the Supplement.

Competing Antiseizure Drug Strategies

We modeled 3 strategies (conservative, moderate, and aggressive) that reflect the plausible range of approaches in the current care of patients with sICH, as well as a risk-guided approach that incorporates risk stratification of early seizure using the 2HELPS2B score into the decision process underlying seizure prophylaxis. eFigure 2 in the Supplement details the application of these 4 strategies in clinical practice.

For simplicity, we used standardized terminology to describe the strategies. Primary prophylaxis was defined as treatment initiated immediately on hospital admission. Secondary prophylaxis was defined as treatment started after a seizure and was further classified as secondary early-seizure prophylaxis (ie, treatment started after a seizure occurring in the first 7 days after the stroke) or secondary late-seizure therapy (ie, treatment started or restarted after a seizure occurring after the first poststroke week). Concerning duration, short-term treatment was defined as a 7-day antiseizure drug course and long-term treatment was defined as indefinite therapy.

Conservative Strategy

In the conservative strategy, patients are monitored for seizures using current guideline recommendations (ie, continuous electroencephalography [cEEG] indicated for those with altered mental status that is out of proportion to the degree

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Table 1. Model Input Parameters

Parameter	Estimate	Sensitivity analysis	Source
Probabilities, %		0-50.0	
Early seizure, cortical involvement			
Yes	19	NA	De Herdt et al,[1] 2011
No	10		
Late seizure, CAVE score			
0	0.6	Base case 1: 3.6% or 9.8%	Haapeniemi et al,[4] 2014
1	3.6	Base case 4: 34.8% or 46.2%	
2	9.8		
3	34.8		
4	46.2		
Antiseizure drug efficacy, %	63	30.0-100.0	Passero et al,[14] 2002
			Consoli et al,[15] 2012
			Rowan et al,[16] 2005
Short-term (7-d) ADR, %	9	0.0-20.0	Inaba et al,[17] 2013
Cumulative lifetime ADR, %	30	20.0-80.0	Consoli et al,[15] 2012
			Kutlu et al,[18] 2008
			García-Escrivá et al,[19] 2007
			Alvarez-Sabín et al,[20] 2002
2HELPS2B score ≥1, %			
Sensitivity	92	Not varied	Moffet et al,[11] 2020
Specificity	49	Not varied	
sICH standardized mortality ratio per year			
First year after stroke	4.73	Not varied	Brønnum-Hansen et al,[21] 2001
After first year	2.31	Not varied	
QOL utilities			
sICH	0.60	Not varied	Lee et al,[22] 2010
Early seizure	0.90	0.0-1.0	Authors' choice
Late seizure	0.79	0.0-1.0	Winter et al,[23] 2018
Refractory seizure	0.75	0.0-1.0	Choi et al,[24] 2008
ADR			
Short-term (7 d)	0.96	0.0-1.0	Authors' choice
Long-term	0.87	0.0-1.0	Moura et al,[25] 2019

Abbreviations: ADR, adverse drug reaction; QOL, quality of life; sICH, spontaneous intracerebral hemorrhage.

of brain injury).[5,13] Patients who develop an early seizure receive short-term secondary early-seizure prophylaxis. Patients subsequently are not given antiseizure drugs, unless they develop recurrent seizures and/or a late seizure, at which point they receive long-term secondary late-seizure therapy.

Moderate Strategy

In the moderate strategy, patients are monitored for seizures using current guideline recommendations.[5,13] Patients receive long-term secondary prophylaxis if they develop an early seizure and long-term secondary therapy if they develop a late seizure.

Aggressive Strategy

In the aggressive strategy, patients receive long-term primary prophylaxis on hospitalization. This occurs regardless of early seizure, late seizure, or ADR development.

Risk-guided Strategy

In the risk-guided strategy, patients undergo a screening EEG for early-seizure risk stratification on admission using the 2HELPS2B score.[10] The 2HELPS2B score estimates early-seizure risk for hospitalized patients using 5 EEG findings and 1 clinical factor (eMethods in the Supplement). The total score is the sum of points assigned to each factor and classifies patients as being at low (0 points), medium (1 point), or high (≥2 points) risk; different seizure risks require distinct EEG monitoring durations (1 hour for low risk; 12 hours for medium risk; and 24 hours for high risk).[10] Patients classified as low risk receive the same antiseizure drug regimen as the conservative strategy. Patients classified as medium or high risk receive short-term primary prophylaxis, which is discontinued 1 week after sICH if they remain seizure free. If patients develop recurrent and/or late seizures, they receive long-term secondary therapy for late seizure.

Model Parameters

Table 1 summarizes the model parameters.[1,4,11,14-25] A detailed description of the ascertainment of model parameters based on prior literature is available in the eMethods in the Supplement.

Model Outcome

The primary outcome was QALYs, a measure of life expectancy factoring in changes in QOL owing to medical conditions (overall QOL utility score × adjusted life expectancy). Quality of life utilities are patient-reported scores based on perceived QOL, with val-

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Table 2. Base Case Parameters

Baseline parameter	Base case 1	2	3	4
Age (life expectancy), y	60.0 (13.8)	80.0 (3.7)	55.0 (17.0)	45.0 (24.7)
Risk, %				
Early seizure	10.0	10.0	19.0	19.0
Late seizure				
Early seizure				
No	3.6	0.6	34.8	34.8
Yes	9.8	3.6	46.2	46.2
ADR risk, %				
Short-term (7 d)	9.0	24.0	9.0	18.0
Long-term (lifetime)	30.0	80.0	30.0	60.0
Utility				
Early seizure	0.90	0.90	0.90	0.90
Late seizure	0.79	0.79	0.79	0.79
Refractory seizure	0.75	0.75	0.75	0.75
ADR				
Short-term (7 d)	0.96	0.90	0.96	0.90
Long-term (lifetime)	0.87	0.40	0.87	0.30

Abbreviation: ADR, adverse drug reaction.

ues varying from 0 (death) and 1 (perfect health). Quality of life utilities represent a subjective measure of perceived disease burden and have been used extensively in previous studies.[26-28] A detailed description of how we ascertained QOL utilities for each medical event (early and late seizures and ADR) is available in the eMethods in the Supplement.

The tree ended in 11 possible health states (eFigure 1 in the Supplement), and the overall QOL utility of each health state was calculated as the product of the utility measures they represent. For example, for a patient with sICH who develops an early seizure, uses a short-term antiseizure drug regimen without developing an ADR, and becomes seizure free for a lifetime uses the following formula:

Overall QOL = uICH × uES and QALYs = age-adjusted life expectancy × uICH × uES where uES indicates utility early seizure and uICH indicates utility ICH. We ascertained life expectancy from age-adjusted standardized mortality ratios after sICH and US mortality data.[12,21] We evaluated competing strategies by comparing accrued QALYs; the preferred treatment strategy was that yielding the greatest QALYs.

Base Cases

We created 4 base cases representing common clinical scenarios with respect to the risks of developing ADRs and late seizure and ADR utility. **Table 2** summarizes the base case parameters.

Base Case 1

A 60-year-old man with low risk of late seizure, average ADR risk and utility, and a history of hypertension is admitted with basal ganglia sICH (6 mL) secondary to hypertensive vasculopathy. His National Institutes of Health Stroke Scale (NIHSS) score is 8 and his ICH score is 0. The bleeding does not involve the cortex (early seizure risk, 10.0%). His CAVE score would be 1 (late seizure risk, 3.6%) if he does not have an early seizure and 2 (late seizure risk, 9.8%) if he does (ie, low seizure risk). He has an average ADR risk (short-term ADR risk, 9.0%; long-term ADR risk, 30.0%) and average ADR utility (short-term ADR utility, 0.96; long-term ADR utility, 0.87). His age-adjusted life expectancy is 13.8 years.

Base Case 2

An 80-year-old woman with a low risk for late seizure, high ADR risk, and low ADR utility presents with a subcortical sICH (8 mL) involving the left parietal lobe secondary to cerebral amyloid angiopathy. Her NIHSS score is 2 and her ICH score is 1. The bleeding does not implicate the cortex (early-seizure risk, 10.0%). Her CAVE score is 0 (late-seizure risk, 0.6%) if she does not develop an early seizure and 1 (late-seizure risk, 3.6%) if she does (ie, low seizure risk). She has multiple comorbidities treated with polypharmacy and a high ADR risk (short-term ADR risk, 24.0%; long-term ADR risk, 80.0%), which imposes a significant decrease in QOL (short-term ADR utility, 0.90; long-term ADR utility, 0.40). Her age-adjusted life expectancy is 3.7 years.

Base Case 3

A 55-year-old man at high risk for late seizure, with average ADR risk and utility, and with a history of hypertension and recreational cocaine use is admitted with lobar sICH (48 mL) with cortical involvement (early-seizure risk, 19.0%). His NIHSS score is 18 and his ICH score is 2. His CAVE score is 3 (late-seizure risk, 34.8%) if he does not have an early seizure and 4 (late-seizure risk, 46.2%) if he does (ie, high seizure risk). He has an average ADR risk (short-term, 9.0%; long-term, 30.0%) and average ADR utility (short-term, 0.96; long-term, 0.87). His age-adjusted life expectancy is 17 years.

Base Case 4

A 45-year-old woman at high risk for late seizure with high ADR risk and low ADR utility presents with lobar sICH (30 mL) and cortical involvement (early-seizure risk, 19.0%). Her NIHSS score is 22 and her ICH score is 2. She has hypertension, chronic kidney disease, and systemic lupus erythematosus. She has

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Figure 1. Primary Outcome: Expected Quality-Adjusted Life-Years (QALYs)

Strategy	Cases			
	1: 60-year-old man with low seizure risk and average ADR risk	**2:** 80-year-old woman with low seizure risk and high ADR risk	**3:** 55-year-old man with high seizure risk and average ADR risk	**4:** 45-year-old woman with high seizure risk and ADR risk
Aggressive	7.88 QALYs	1.15 QALYs	9.21 QALYs[a]	8.08 QALYs
Moderate	8.07 QALYs	2.09 QALYs	8.93 QALYs	10.93 QALYs
Conservative	8.08 QALYs	2.18 QALYs[a]	8.77 QALYs	11.23 QALYs
Risk guided	8.13 QALYs[a]	2.17 QALYs	8.98 QALYs	11.53 QALYs[a]

Main results of each treatment strategy for each clinical scenario. For scenario 1, the risk-guided strategy was preferred by 0.05 QALYs compared with the conservative strategy (second-most preferred strategy). For scenario 2, the conservative strategy was preferred by a net difference of 0.01 QALYs compared with the risk-guided strategy (second-most preferred strategy), which was preferred by 0.08 QALYs compared with the moderate strategy (third-most preferred strategy). For scenario 3, the aggressive strategy was preferred by 0.23 QALYs compared with the risk-guided strategy (second-most preferred strategy). For scenario 4, the risk-guided strategy was preferred by 0.30 QALYs compared with the conservative strategy (second-most preferred strategy). ADR indicates adverse (antiseizure) drug reaction.

[a] Preferred strategy for the scenario.

high ADR risk (short-term, 18.0%; long-term, 60.0%), which would significantly decrease her QOL (short-term ADR utility, 0.90; lifetime ADR utility, 0.30). Her CAVE score is 3 (late-seizure risk, 34.8%) if she does not have an early seizure and 4 (late-seizure risk, 46.2%) if she does (ie, high seizure risk). Her age-adjusted life-expectancy is 24.7 years.

Model Assumptions

We made several simplifying assumptions in our model. First, given the absence of data on late-seizure risk for longer periods, we assumed that the lifetime late-seizure risk was the same as the CAVE-derived risk. Second, we assumed that patients would adhere to the prescribed prophylaxis strategy regardless of the development of ADRs. Third, sICH, ADR, early seizures, late seizures, and refractory seizures all exerted an average, constant QOL decrement throughout the patient's lifetime that is captured by their mean patient-preference utility values (ie, for ICH, short-term ADR, long-term ADR, early seizure, late seizure, and refractory seizure).

Sensitivity Analyses

We addressed the uncertainty around our assumed parameters by conducting several sensitivity analyses. We selected ranges of parameter values based on expert opinion and a review of the literature (Table 1) and performed these analyses using base cases 1 and 4 because they represent patients with low and high risks for late seizure. We conducted 1-way sensitivity analyses by varying early-seizure risk, antiseizure drug efficacy, cumulative ADR risk, and the utilities of early seizure, late seizure, refractory seizure, and ADRs (short- and long-term). We conducted three 2-way sensitivity analyses: (1) long-term ADR risk and utility of long-term ADR risk; (2) long-term ADR risk and early-seizure risk, and (3) long-term ADR risk and antiseizure drug efficacy. Because data from patients with traumatic brain injury suggest that prophylactic antiseizure drugs do not reduce the risk of a first-time late seizure,[29] we performed a sensitivity analysis considering antiseizure drug efficacy to be null for the prevention of incident late seizure.

Results

Figure 1 summarizes the results for each base case analysis. For base case 1, a man who had a low risk for late seizure and average risk and utility for ADR, 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 base case 2, a woman who had a low risk for late seizure but high ADR risk and low ADR utility, 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 base case 3, a man who had a high risk for late seizure and average ADR risk and utility, 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 base case 4, a woman who had a high risk for late seizure, high ADR probability, and very low ADR utility, 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 (**Figure 2**, **Figure 3**, and eFigures 3-5 in the Supplement) indicated that the risk-guided strategy performed comparably to or better than alternative strategies in a wide range of settings. The aggressive strategy was preferred in limited settings where the late-seizure risk was high (as in base cases 3 and 4), the long-term ADR risk was lower (Figure 3), and, based mostly on patient preference, long-term ADR utilities were closer to 1 (perfect health) (ie, the patient perceives that long-term ADR would minimally affect his or her QOL). Finally, a sensitivity analysis considering antiseizure drugs to have no effect in preventing incident late seizure revealed that the risk-guided strategy was preferred in scenarios 1, 3, and 4, whereas the conservative strategy was preferred in scenario 2 (eFigure 6 in the Supplement). In this analysis, the net QALY differences between the risk-guided and alternative strategies were higher (eFigure 6 in the Supplement).

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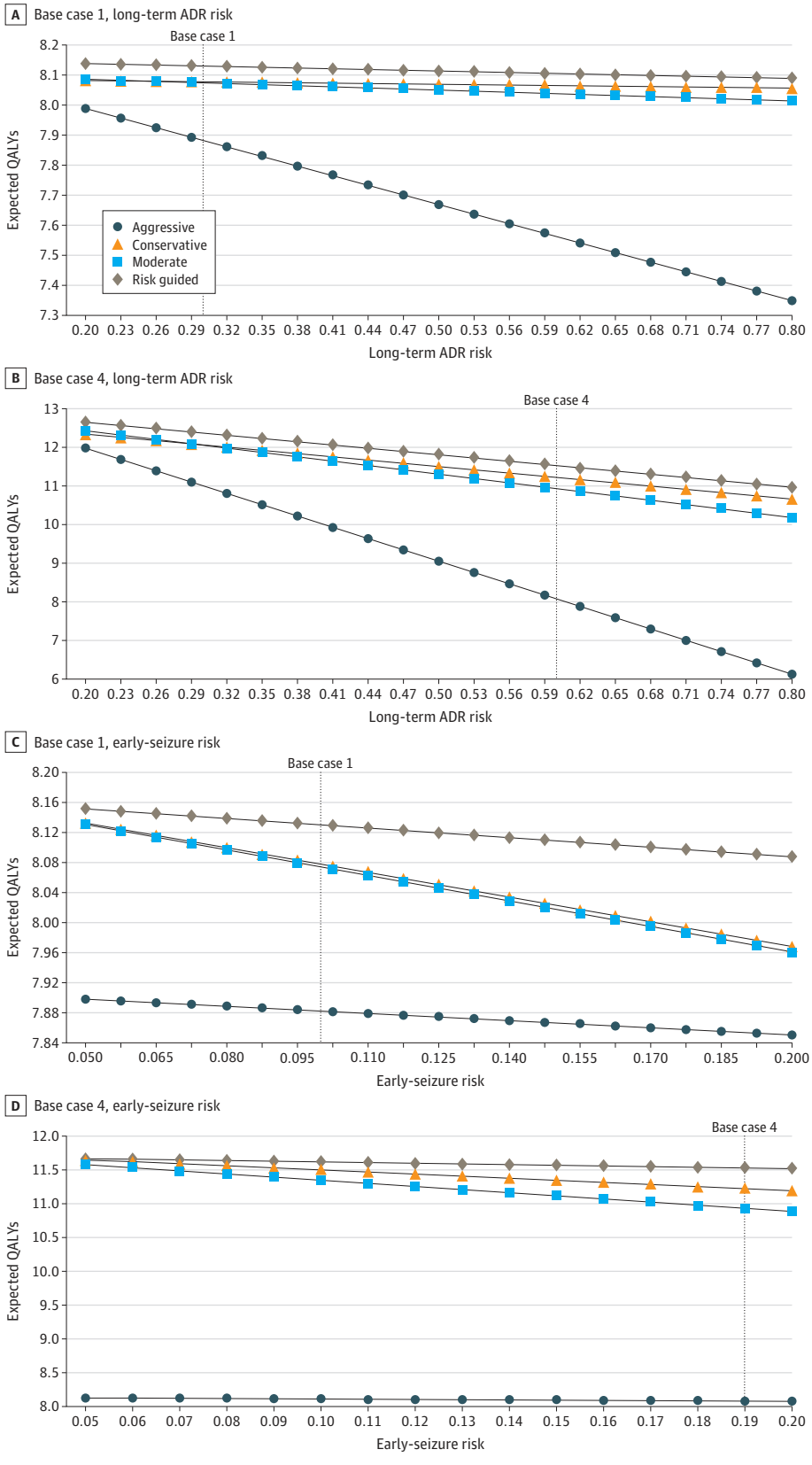
Figure 2. Sensitivity Analysis: Long-term Adverse Drug Reaction (ADR) and Early-Seizure Risks



One-way sensitivity analyses performed on base cases 1 and 4 assessed the boundaries of our estimates under clinically plausible scenarios. A and B, The risk-guided strategy was preferred over the entire range of plausible values (20%-80%) for long-term ADR risk. C and D, The risk-guided strategy was preferred over the range of plausible values (5%-20%) for early-seizure risk. QALYs indicates quality-adjusted life-years.

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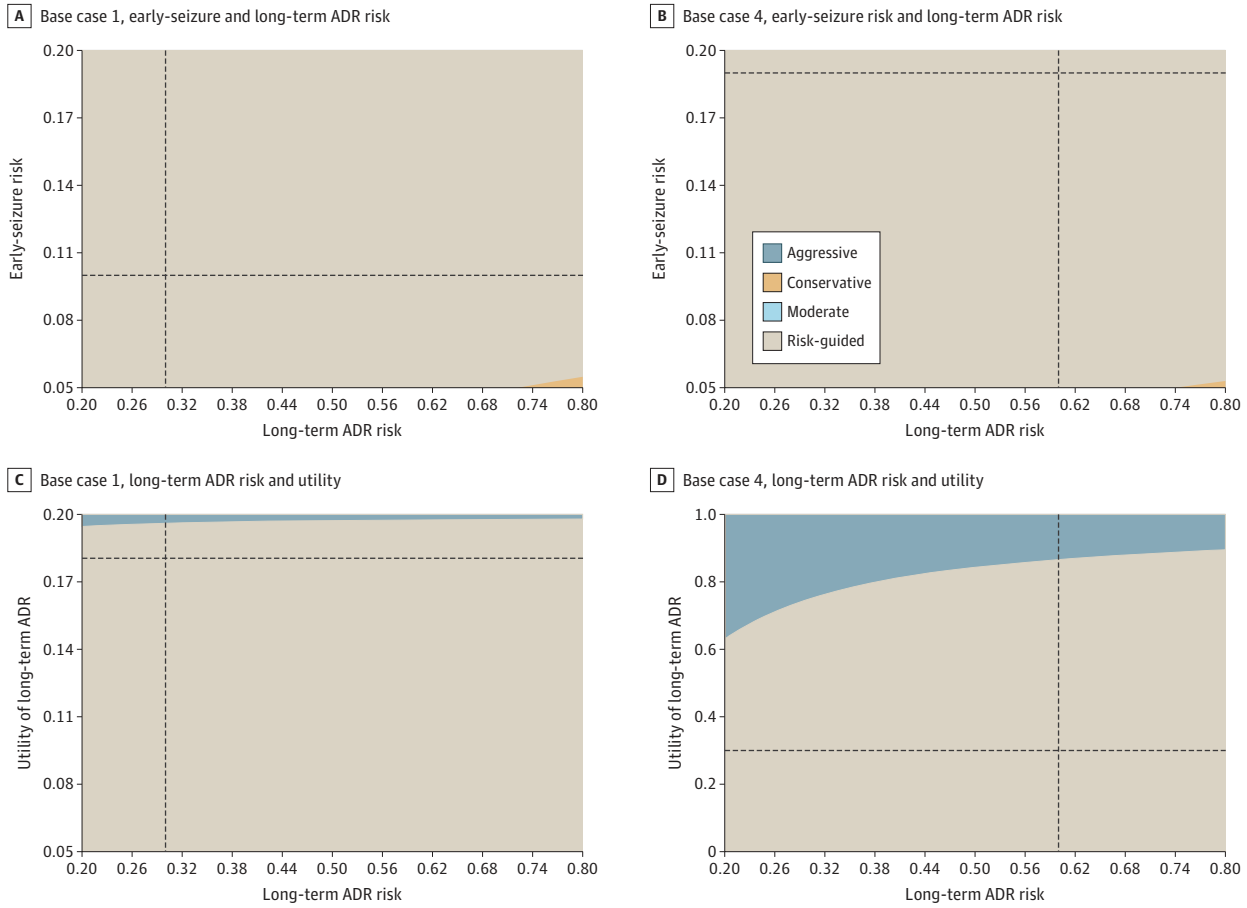
Figure 3. Sensitivity Analysis: Long-term Adverse Drug Reaction (ADR) Risk, Early-Seizure Risk, and Long-term ADR Utility



Two-way sensitivity analyses performed on base cases 1 and 4 assessed the boundaries of our estimates under clinically plausible scenarios. A and B, The risk-guided strategy was preferred over the entire combined range of plausible values for early-seizure risk (5%-20%) and long-term ADR risk (20%-80%). C and D, The risk-guided strategy was preferred over most combinations of plausible values for long-term ADR risk (20%-80%) and long-term ADR utility (0-1.0); the aggressive strategy was preferred for higher long-term ADR utilities, especially in scenarios in which the late-seizure risk is high (base case 4) and the long-term ADR risk is lower.

Discussion

We used a decision analytical model to examine the net benefit of 4 antiseizure drug prophylaxis strategies across 4 common base cases starting from presentation with incident sICH. We found short-term (7 days) early-seizure prophylactic regimens are preferred over long-term (lifelong) regimens under most realistic clinical scenarios. Our results also suggest that a strategy that incorporates an early-seizure risk stratification tool (2HELPS2B) to identify patients most likely to benefit from short-term primary vs secondary early-seizure prophylaxis is favored over alternative strategies in most settings.

Overall, strategies that involve long-term antiseizure drug prescription (ie, moderate and aggressive) fail to provide better outcomes in most clinical scenarios when compared with strategies using short-term regimens (ie, conservative and risk guided). In fact, given the limited understanding of long-term safety profiles of antiseizure drugs, long-term antiseizure drug regimens (moderate and aggressive) potentially pose notable risks. This finding contradicts patterns of prolonged antiseizure drug use that can be seen in some clinical practices. For example, some physicians prescribe long-term antiseizure drug regimens for patients considered high risk for poststroke epilepsy. In addition, some patients may continue medication regimens indefinitely (eg, a form of polypharmacy), even when long-term prophylaxis was not the original intent of the first prescribing physician, perhaps because continued coordination of care involving different settings (ie, hospitals, clinics, and rehabilitation) and close seizure and ADR monitoring could be challenging. Therefore, our findings underscore the importance of early discontinuation of antiseizure drug regimens initiated before or after an early seizure (eg, with explicit stopping dates written into the original prescription, patient materials, and discharge communication), unless there is a clear patient preference behind this regimen (eg, the patient perceives that long-term ADRs would minimally affect his or her QOL).

Contrary to current guidelines,[5] our results indicate that short-term primary early-seizure prophylaxis has a role in the

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management of sICH in high-risk patients (2HELPS2B score, ≥1). Proponents of primary prophylaxis argue that previous investigations reporting worse outcomes[30,31] were confounded by treatment indication and that those findings may not apply to new-generation antiseizure drugs (eg, levetiracetam) due to a potentially safer profile over phenytoin.[32,33] Moreover, some perceive seizures as a highly detrimental event in the acute care setting because they can lead to hematoma expansion,[3] neuronal injury,[34] and clinical decompensation.[3] As evidence accumulates suggesting some EEG epileptiform abnormalities (ie, interictal-ictal continuum) are associated with high seizure risk,[11,35,36] some clinicians might see primary prophylaxis as advantageous in these situations. Indeed, it is not surprising that short-term primary prophylaxis would be beneficial for patients at high risk for disease complications; this decision analysis provides a way to quantify this threshold of high risk using an established risk calculator (2HELPS2B).

Taken together, our results underscore that a risk-guided approach to seizure prophylaxis using an EEG-based seizure risk stratification tool (2HELPS2B) can aid physicians in identifying patients most likely to benefit from short-term primary prophylaxis for early seizure. For instance, short-term primary prophylaxis is justifiable in the small number of patients with higher risk scores (2HELPS2B score, ≥1), whereas only secondary early-seizure prophylaxis is justifiable for most patients with lower risk scores (2HELPS2B score, 0) (ie, primary prophylaxis not recommended). However, if timely access to EEG is unavailable for early-seizure risk stratification, the conservative strategy appears the most reasonable, and clinicians should avoid primary prophylaxis for most patients in that setting. The exception to this rule would be patients at higher risk of late seizure (ie, CAVE score, ≥3) and lower long-term ADR risks (eg, younger with fewer comorbidities and comedications), for whom the aggressive strategy might be considered based on their preference (ie, the patient's assessment of QOL utility of potential long-term ADR).

Limitations

We recognize several limitations of our study. Because we used the published literature to obtain data to estimate our model parameters, our estimates might be biased. Our estimates of antiseizure drug efficacy and ADR, for example, were taken from studies without direct comparisons between antiseizure drugs and no intervention.[14-20] We attempted to address these parameter uncertainties via sensitivity analyses.

In addition, we did not account for other possible factors that could modify some parameter estimates. Surgical treatment, hematoma expansion, and sICH recurrence, for example, are risk factors associated with early and late seizures.[37] However, our sensitivity analyses suggest that increasing risks for early and late seizure favor the risk-guided strategy.

Finally, we assumed that patients would adhere to the prescribed strategies regardless of ADR and did not account for factors that may influence medication adherence such as socioeconomic factors and comorbidities. In a realistic setting, however, poor medication adherence is relatively common among antiseizure drug users and negatively affects therapy effectiveness.[38] Nonetheless, our sensitivity analyses indicated that varying antiseizure drug efficacy does not have an important influence on preferred strategies.

Conclusions

Our decision analysis indicates the advantages of short-term (7-day) antiseizure drug strategies across a spectrum of clinical scenarios for patients presenting with incident sICH. This finding underscores the importance of early discontinuation of antiseizure drug strategies initiated for early-seizure prophylaxis. Moreover, we recommend a risk-based approach using the 2HELPS2B score to guide clinical decision on initiation of primary vs secondary early-seizure prophylaxis for all patients after sICH, assuming timely availability of EEG.

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