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ORIGINAL WORK

Antiseizure Medication Treatment and Outcomes in Patients with Subarachnoid Hemorrhage Undergoing Continuous EEG Monitoring

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Abstract

Background: Patients with aneurysmal subarachnoid hemorrhage (aSAH) with electroencephalographic epileptiform activity (seizures, periodic and rhythmic patterns, and sporadic discharges) are frequently treated with antiseizure medications (ASMs). However, the safety and effectiveness of ASM treatment for epileptiform activity has not been established. We used observational data to investigate the effectiveness of ASM treatment in patients with aSAH undergoing continuous electroencephalography (cEEG) to develop a causal hypothesis for testing in prospective trials.

Methods: This was a retrospective single-center cohort study of patients with aSAH admitted between 2011 and 2016. Patients underwent ≥ 24 h of cEEG within 4 days of admission. All patients received primary ASM prophylaxis until aneurysm treatment (typically within 24 h of admission). Treatment exposure was defined as reinitiation of ASMs after aneurysm treatment and cEEG initiation. We excluded patients with non-cEEG indications for ASMs (e.g., epilepsy, acute symptomatic seizures). Outcomes measures were 90-day mortality and good functional outcome (modified Rankin Scale scores 0–3). Propensity scores were used to adjust for baseline covariates and disease severity.

Results: Ninety-four patients were eligible (40 continued ASM treatment; 54 received prophylaxis only). ASM continuation was not significantly associated with higher 90-day mortality (propensity-adjusted hazard ratio [HR] = 2.01 [95% confidence interval (CI) 0.57–7.02]). ASM continuation was associated with lower likelihood for 90-day good functional outcome (propensity-adjusted HR = 0.39 [95% CI 0.18–0.81]). In a secondary analysis, low-intensity treatment (low-dose single ASM) was not significantly associated with mortality (propensity-adjusted HR = 0.60 [95% CI 0.10–3.59]), although it was associated with a lower likelihood of good outcome (propensity-adjusted HR = 0.37 [95% CI 0.15–0.91]), compared with prophylaxis. High-intensity treatment (high-dose single ASM, multiple ASMs, or anesthetics) was associated with higher mortality (propensity-adjusted HR = 6.80 [95% CI 1.67–27.65]) and lower likelihood for good outcomes (propensity-adjusted HR = 0.30 [95% CI 0.10–0.94]) compared with prophylaxis only.

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Conclusions: Our findings suggest the testable hypothesis that continuing ASMs in patients with aSAH with cEEG abnormalities does not improve functional outcomes. This hypothesis should be tested in prospective randomized studies.

Keywords: Subarachnoid hemorrhage, Electroencephalography, Anticonvulsants, Seizures, Outcome assessment

Introduction

Patients with aneurysmal subarachnoid hemorrhage (aSAH) with electroencephalographic epileptiform activity (seizures, periodic and rhythmic patterns, and sporadic discharges) are frequently treated with antiseizure medications (ASMs) [1, 2]. Despite mounting evidence that epileptiform activity is associated with worse outcomes, there are limited data to guide treatment [2, 3]. Primary prophylaxis with ASMs is associated with worse cognitive and functional outcomes in patients with aSAH [4, 5]. Standardized guidelines, therefore, do not recommend primary prophylaxis beyond the immediate posthemorrhage period [6]. Nevertheless, ASMs are commonly prescribed in patients with aSAH when epileptiform activity is detected, with the rationale of preventing seizures and secondary brain injury. However, the safety and effectiveness of prescribing ASMs in patients with aSAH with epileptiform activity has not been established [2, 3].

We hypothesized that use of ASMs to treat epileptiform activity in aSAH often causes net harm, increasing mortality and worsening functional outcomes. Although a randomized clinical trial would be needed to test this hypothesis definitively, here we sought to develop preliminary support for the hypothesis through analysis of existing observational data to evaluate the safety and effectiveness of ASM treatment in patients with aSAH undergoing continuous electroencephalography (cEEG) monitoring. We used strict inclusion and exclusion criteria and propensity methodology to investigate the association of ASM treatment for epileptiform activity with survival and functional outcomes.

Methods

This is a retrospective cohort study of patients with aSAH admitted at our center between September 2011 and February 2016. The data that support the findings of this study are available from the corresponding author (SFZ), on reasonable request. The study was approved by the Institutional Review Board of Mass General Brigham. Informed consent was not required for this retrospective study. There were four main eligibility criteria: (1) admission for treatment of aSAH, (2) age > 18 years, (3) cEEG monitoring initiated within 4 days of admission, and (4) ≥ 24 h of cEEG monitoring. We restricted inclusion to patients with cEEG beginning within 4 days of admission because the majority of patients develop epileptiform activity during this period [7]. To increase homogeneity of the cohort, we excluded patients likely to receive ASMs regardless of EEG findings, e.g., a history of epilepsy or acute symptomatic clinical seizures on admission.

All patients received primary ASM prophylaxis until the aneurysm was secured on the basis of institutional protocol and consensus guidelines [6]. The aneurysm is typically treated within the first 24 h of admission, and primary prophylaxis is discontinued immediately thereafter, unless the patient undergoes craniectomy or craniotomy, in which case primary prophylaxis is continued at the treating team's discretion. We excluded patients who were continued on primary ASM prophylaxis after the aneurysm was secured for the indication of craniectomy or craniotomy, regardless of EEG findings. Figure 1 displays the inclusion and exclusion flowchart.

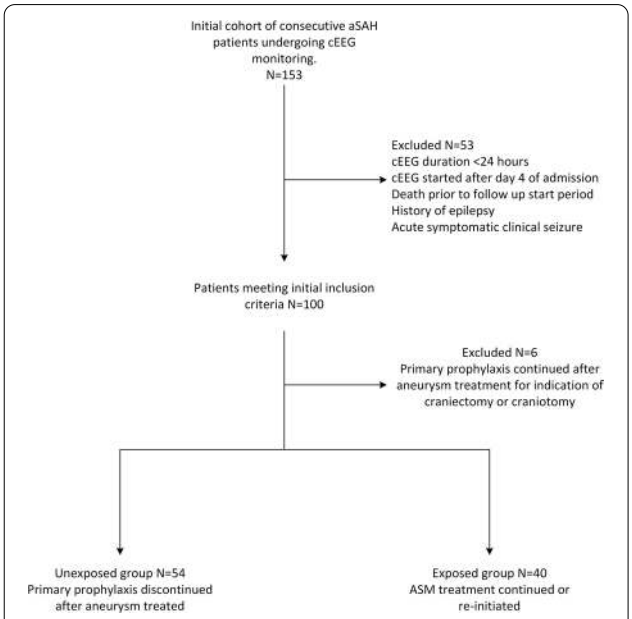

Fig. 1 Patient selection process. A graphical description of the inclusion and exclusion criteria and exposed and unexposed groups is provided. *aSAH* aneurysmal subarachnoid hemorrhage, *ASM* antiseizure medication, *cEEG* continuous electroencephalography

Exposure Definition

We compared patients who received prophylactic therapy only versus those who continued ASM therapy. Levetiracetam at a dose of 1000 mg/day is the standard prophylactic dose per institutional protocol. We defined ASM treatment exposure as continuation or reinitiation of ASMs for > 48 h after aneurysm treatment and 24 h after initiation of cEEG through day 10 of admission (Fig. 2). We used this exposure window because the likelihood of developing epileptiform activity is highest within the first 5 days of admission and decreases after day 10 of admission [7]. In addition, the highest risk of delayed cerebral ischemia (DCI), which is closely associated with epileptiform activity, is within the first 10 days after aSAH [7–9]. The unexposed group consisted of patients who only received primary ASM prophylaxis until the aneurysm was secured.

In secondary analyses, we classified continued ASM therapy into two groups:

1. *Low-intensity treatment* defined as continuation or reinitiation of monotherapy with one of the following ASMs: a) levetiracetam at a dose of < 2000 mg/day (< 1000 mg/day in patients with renal dysfunction), b) phenytoin with mean serum levels of < 15 μg/mL or a dose of ≤ 300 mg/day if no serum levels are available, c) valproic acid with mean serum levels of < 75 μg/mL or a dose of ≤ 15 mg/kg/day if no serum levels are available, or d) lacosamide at ≤ 200 mg/day
2. *High-intensity treatment* defined as treatment with any of the following: a) levetiracetam at a dose of ≥ 2000 mg/day (≥ 1000 mg/day in patients with renal dysfunction), b) phenytoin with mean serum levels of ≥ 15 μg/mL or a dose of > 300 mg/day if no levels are available, c) valproic acid with mean serum levels of ≥ 75 μg/mL or a dose of > 15 mg/kg/day if no levels are available, d) lacosamide at > 200 mg/day, e) use of two or more ASMs, or f) initiation of anesthetics for treatment of epileptiform activity.

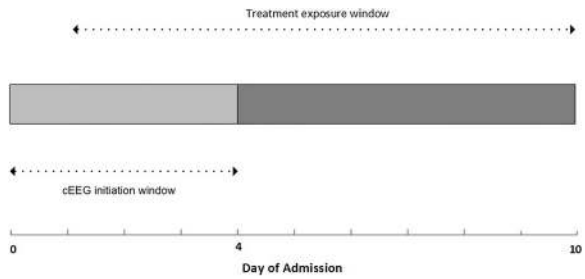

Fig. 2 EEG and treatment exposure windows. All cEEGs were performed within 4 days of admission and were at least 24 h in duration. Treatment exposure window: 24 h post EEG to up to day 10 of admission. Unexposed group: ASM prophylaxis only. Exposed group: ASM continuation or reinitiation for > 48 h. Low intensity treatment: monotherapy with levetiracetam at a dose of < 2000 mg/day (< 1000 mg/day in impaired renal function), phenytoin at ≤ 300 mg/day or mean level of < 15 μg/mL, valproic acid at ≤ 15 mg/kg/day or mean level of < 75 μg/mL, or lacosamide at ≤ 200 mg/day. High intensity treatment: > 48 h of levetiracetam at a dose of ≥ 2000 mg/day (≥ 1000 mg/day in impaired renal function), phenytoin at > 300 mg/day or mean level of ≥ 15 μg/mL, valproic acid at > 15 mg/kg/day or mean level of ≥ 75 μg/mL, lacosamide > 200 mg/day, use of two or more ASMs, or initiation of anesthetics for treatment of epileptiform activity. *ASM* antiseizure medication, *cEEG* continuous electroencephalography

Follow up for outcomes started after day 10 of admission and continued in an intention-to-treat scheme until 100 days post admission (or 90 days from the start of follow-up).

Clinical Covariates

We collected demographic and clinical variables from the electronic health record. We calculated critical illness severity, e.g., admission Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [10], and aSAH severity scores, e.g., Hunt and Hess, Fisher, and Functional Recovery Expected after Subarachnoid Hemorrhage (FRESH) scores [11–13]. The FRESH score predicts long-term outcomes and comprises age, Hunt and Hess score, physiologic APACHE II score, and presence of rebleed [13]. The Charlson Comorbidity Index (CCI) was calculated as an integrated measure of baseline chronic health conditions [14]. Delayed complications, including DCI and hospital-acquired infections, were recorded. Methods for DCI adjudication have been previously published [2, 15].

EEG Features

Methods for reviewing and reporting EEGs, classifying epileptiform activity, and quantifying burden of epileptiform activity have been previously published [2]. At our center, all patients with high-grade aSAH (Hunt and Hess score ≥ 3 or Fisher score ≥ 3) undergo cEEG monitoring for ischemia detection. Additional indications for cEEG monitoring include evaluation for subclinical seizures and monitoring the depth of sedation.

We defined epileptiform activity using the American Clinical Neurophysiology Society (ACNS) nomenclature [16]. We included the following patterns in our definition of epileptiform activity: lateralized periodic discharges, bilateral independent periodic discharges, generalized periodic discharges, lateralized rhythmic delta activity, and sporadic discharges. Epileptiform activity burden was quantified by using the ACNS nomenclature: rare, < 1%; occasional, 1–9%; frequent, 10–49%; abundant, 50–89%;

and continuous, ≥ 90% [16]. Epileptiform activity burden was calculated for the first 24 h of recording, and the maximum burden (peak burden) was calculated within any 24-h epoch, as previously described [2].

Mortality and Functional Outcomes

Primary outcomes were 90-day mortality and 90-day modified Rankin Scale (mRS) score. The mRS is a 6-point scale: 0, no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, dead [17, 18]. The mRS score was abstracted from physician and physical therapy clinical examinations by three reviewers (MAA, PS, SR) who were blinded to the EEG findings and ASM treatment. Good outcome was defined as mRS scores 0–3, and poor outcome was defined as mRS scores 4–6.

Additional Outcomes

We also collected information on the occurrence of in-hospital ASM-specific adverse effects through the same electronic health record chart abstraction (see Supplemental Table 1). In addition, we measured the time to sustained EEG improvement, defined as time taken (in hours) for peak burden to decrease to a lower level as measured by ACNS criteria and be sustained at a lower level for > 48 h. We also examined time to late-onset (after postbleed day 14) clinical seizures.

Statistical Analysis

Univariate analysis was performed by using Fisher's exact test for dichotomized and categorical variables and the Mann–Whitney *U*-test for continuous variables. Significance was set at 0.05, and two-sided *P* values are reported. Equality of survival functions was assessed by using the log-rank test.

To adjust for potential differences between patients receiving prophylactic versus continued ASM therapy, we calculated propensity scores for continued therapy using logistic regression models. The propensity score regression models included variables likely to be associated with ASM treatment, predictors of poor functional outcome, and risk factors associated with DCI [2, 3, 11–13, 19, 20]. Variables selected for the propensity score captured illness severity, EEG findings, and comorbidities and were measured prior to the exposure window. The following variables were included in the propensity score regression model for the primary analysis: CCI, FRESH score, Fisher score, and first 24-h epileptiform activity burden. We used the FRESH score in our propensity model instead of the individual components to avoid overfitting the model. The outcome/dependent variable in the propensity score logistic regression model was ASM treatment exposure. The area under the receiver operating characteristic curve (for the propensity score regression model for the primary analysis was 0.80.

In secondary analyses, we performed pairwise comparisons assessing ASM treatment intensity. Three separate propensity scores were built to estimate the likelihood of (1) low-intensity ASM treatment vs. prophylaxis only, (2) high-intensity treatment vs. prophylaxis only, and (3) high-intensity ASM treatment vs. low-intensity treatment. Independent variables included in each of the models were the following: CCI, FRESH score, Fisher score, and the first 24-h epileptiform activity burden. Performance of the propensity score regression models was assessed by using the area under the receiver operating characteristic curve: low-intensity treatment vs. prophylaxis only, 0.76; high-intensity treatment vs. prophylaxis only, 0.87; high-intensity vs. low intensity treatment, 0.76.

For each primary and secondary analysis, the corresponding estimated propensity score was included in a Cox proportional hazard model to assess the association between ASM treatment and outcomes. The proportional hazards assumption was checked by using Schoenfeld residuals and log–log survival plots. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Patients lost to follow-up were right censored in the analysis.

Results

Overall, 94 patients met inclusion criteria; 54 (57.4%) patients received prophylaxis only, and 40 (42.6%) either continued or reinitiated ASM treatment (combined low and high intensity). Patients in the prophylaxis only group received a median of 24 h of ASMs (interquartile range 24–24). Patients who were continued on treatment received a median of 14 days of inpatient ASM treatment (interquartile range 11–20). Of the 31 patients who were continued on treatment who were alive at discharge, 20 (64.5%) were discharged with ASM prescriptions. Table 1 summarizes the clinical and demographic characteristics. There were no missing data. Patients continuing or reinitiating ASM treatment were likely to have higher APACHE II (16 [11–21] vs. 11 [7–18], $p = 0.035$) and FRESH scores (4.4 [3.7–6.1] vs. 3 [1.8–4.4], $p = 0.003$) compared with patients receiving ASM prophylaxis only. Patients treated with ASMs were also more likely to have epileptiform activity, with higher first 24-h and peak burdens. Peak burden was defined as the epileptiform activity burden in the 24-h epoch with the highest burden.

Table 2 summarizes disease severity and epileptiform activity burden across the three levels of treatment intensity. All patients in the low-intensity group received levetiracetam at < 2000 mg/day and had preserved renal function. In the high-intensity group, 16 (94.1%) received levetiracetam at > 2000 mg/day, 2 (11.8%) received phenytoin

Table 1 Clinical and demographic variables

	Prophylaxis only ($n=54$)	ASM treatment (low + high intensity) ($n=40$)	p value
Age, median (IQR)	57 (49–68)	60 (57–73)	0.243
Sex, female	42 (78%)	29 (73%)	0.556
CCI, median (IQR)	2 (1–3)	2 (1–3)	0.447
APACHE II, median (IQR)	11 (7–18)	16 (11–21)	**0.035**
Hunt and Hess score			**0.028**
1	15 (28%)	4 (10%)	
2	9 (17%)	11 (28%)	
3	15 (28%)	6 (15%)	
4	12 (22%)	11 (28%)	
5	3 (6%)	8 (20%)	
Fisher score			0.244
1	0 (0%)	0 (0%)	
2	6 (11%)	2 (5%)	
3	42 (78%)	29 (73%)	
4	6 (11%)	9 (23%)	
FRESH score, median (IQR)	3 (1.9–4.4)	4.4 (3.0–6.1)	**0.003**
Treatment modality			0.699
Coil	32 (59%)	19 (48%)	
Clip	19 (35%)	19 (48%)	
Clip plus coil	1 (2%)	1 (3%)	
Flow diverter	1 (2%)	1 (3%)	
Flow diverter plus coil	1 (2%)	0 (0%)	
Rebleed	0 (0%)	9 (23%)	**< 0.0001**
Delayed cerebral ischemia	25 (46%)	30 (75%)	0.006
Days to EEG start, median (IQR)	2 (1–3)	2 (1–2)	0.820
EEG duration in days, median (IQR)	6.6 (4.8–8.8)	8.7 (6.9–9.7)	**0.005**
First 24-h epileptiform activity burden			**< 0.0001**
None	46 (85%)	20 (50%)	
Rare (< 1%)	5 (9%)	3 (8%)	
Occasional (1–9%)	1 (2%)	4 (10%)	
Frequent (10–49%)	0 (0%)	3 (8%)	
Abundant (50–89%)	2 (4%)	9 (23%)	
Continuous (> 90%)	0 (0%)	1 (3%)	
Peak epileptiform activity burden			**< 0.0001**
None	38 (70%)	8 (20%)	
Rare (< 1%)	6 (11%)	3 (8%)	
Occasional (1–9%)	5 (9%)	4 (10%)	
Frequent (10–49%)	2 (4%)	9 (23%)	
Abundant (50–89%)	3 (6%)	9 (23%)	
Continuous (> 90%)	0 (0%)	7 (18%)	
Hospital-acquired pneumonia	19 (35%)	22 (55%)	0.062
Duration of mechanical ventilation in days, median (IQR)	0 (0–3)	10.5 (4–15.5)	**< 0.0001**
ICU length of stay in days, median (IQR)	14.5 (11–17)	18 (15–22)	**0.0004**

APACHE II Acute Physiology and Chronic Health Evaluation II, *CCI* Charlson Comorbidity Index, *EEG* electroencephalography, *FRESH* Functional Recovery Expected after Subarachnoid Hemorrhage, *ICU* intensive care unit, *IQR* interquartile range

Bolded values indicate $p < 0.05$

Table 2 Clinical variables across levels of treatment intensity

	Prophylaxis only ($n=54$)	Low-intensity treatment ($n=23$)	p value
Prophylaxis only versus low-intensity treatment			
Age, median (IQR)	57 (49–68)	65 (50–78)	0.109
CCI, median (IQR)	2 (1–3)	3 (1–4)	0.140
Fisher score			0.225
1	0 (0%)	0 (0%)	
2	6 (11%)	0 (0%)	
3	42 (78%)	19 (83%)	
4	6 (11%)	4 (17%)	
FRESH score, median (IQR)	3 (2–4)	5 (4–6)	**0.008**
First 24-h epileptiform activity burden			0.078
None	46 (85%)	15 (65%)	
Rare	5 (9%)	2 (9%)	
Occasional	1 (2%)	2 (9%)	
Frequent	0 (0%)	0 (0%)	
Abundant	2 (4%)	3 (13%)	
Continuous	0 (0%)	1 (4%)	
	Prophylaxis only ($n=54$)	**High-intensity treatment ($n=17$)**	***p* value**
Prophylaxis only versus high-intensity treatment			
Age, median (IQR)	57 (49–68)	59 (51–64)	0.909
CCI, median (IQR)	2 (1–3)	2 (1–2)	0.654
Fisher score			0.163
1	0 (0%)	0 (0%)	
2	6 (11%)	2 (12%)	
3	42 (78%)	10 (56%)	
4	6 (11%)	5 (29%)	
FRESH score, median (IQR)	3 (2–4)	4 (4–6)	**0.043**
First 24-h epileptiform activity burden			**< 0.001**
None	46 (85%)	5 (29%)	
Rare	5 (9%)	1 (6%)	
Occasional	1 (2%)	2 (12%)	
Frequent	0 (0%)	3 (18%)	
Abundant	2 (4%)	6 (35%)	
Continuous	0 (0%)	0 (0%)	
	Low-intensity treatment ($n=23$)	**High-intensity treatment ($n=17$)**	***p* value**
Low-intensity versus high-intensity treatment			
Age, median (IQR)	65 (50–78)	59 (51–64)	0.191
CCI, median (IQR)	3 (1–4)	2 (1–2)	0.072
Fisher score			0.119
1	0 (0%)	0 (0%)	
2	0 (0%)	2 (12%)	
3	19 (83%)	10 (56%)	
4	4 (17%)	5 (29%)	
FRESH score, median (IQR)	5 (4–6)	4 (4–6)	0.528
First 24-h epileptiform activity burden			0.053
None	15 (65%)	5 (29%)	
Rare	2 (9%)	1 (6%)	
Occasional	2 (9%)	2 (12%)	
Frequent	0 (0%)	3 (18%)	

Table 2 (continued)

	Low-intensity treatment ($n=23$)	High-intensity treatment ($n=17$)	p value
Abundant	3 (13%)	6 (35%)	
Continuous	1 (4%)	0 (0%)	

CCI Charlson Comorbidity Index, *FRESH* Functional Recovery Expected after Subarachnoid Hemorrhage, *IQR* interquartile range

Bolded values indicate $p < 0.05$

at > 300 mg/day (mean serum level of 15.4 µg/mL and peak levels of 17.4 and 22.1 µg/mL), 1 (6.8%) received lacosamide at > 200 mg/day, 6 (37.5%) received multiple ASMs, and 1 (6.8%) received anesthetics for treatment of cEEG findings (these percentages are not mutually exclusive).

Although limited by retrospective chart review, we attempted to examine the indications for ASM treatment exposure. Among the ASM treatment exposure group, we found that in 26 of 32 (82%) patients with epileptiform activities, there was clear documentation of ASMs being continued or reinitiated in response to cEEG epileptiform activity. In the remaining six patients with epileptiform activity within the exposure group, the indication for ASM continuation or initiation was not clearly documented. Among the eight patients in the ASM treatment exposure group with no epileptiform activity, two were treated for generalized rhythmic slowing and one was treated for potential risk of alcohol withdrawal seizure. Indication for continuation and/or initiation of ASMs in the remaining five patients was not clearly documented.

Relative Hazards of Primary Outcomes

Figure 3a, b shows the unadjusted and adjusted survival curves. At 90 days, mortality was 9 of 40 (23%) in the ASM continuation group and 5 of 54 (9%) in the prophylaxis only group. All patients with mortality had life-sustaining therapy withheld or were discharged to hospice. The unadjusted HR for 90-day mortality in the ASM treatment group was 2.83 (95% CI 0.95–8.45). After adjustment for the propensity score, the HR remained elevated, although CIs included the null hypothesis value (HR 2.01 [95% CI 0.57–7.02]).

Figure 3c, d shows the unadjusted and adjusted survival curves for good outcome, which was defined as mRS scores 0–3. At 90 days, 12 (30%) patients in the ASM continuation group had good functional outcome versus 38 (70%) in the prophylaxis only group. The unadjusted HR for good functional outcome in the ASM treatment group compared with the ASM prophylaxis only group was 0.25 (95% CI 0.13–0.48). After adjustment for the propensity score, ASM treatment continued to be associated with lower likelihood for good functional outcome at 90 days (HR 0.39 [95% CI 0.18–0.81]). Survival data, including loss to follow-up rates, are summarized in Supplemental Tables 2 and 3.

Within pairwise comparisons, there was no significant difference in 90-day survival when comparing low-intensity treatment with prophylaxis (adjusted HR 0.60 [95% CI 0.10–3.59]). High-intensity treatment was associated with higher 90-day mortality compared with both prophylaxis (adjusted HR 6.80 [95% CI: 1.67–27.65]) and low-intensity treatment (adjusted HR 9.79 [95% CI 1.75–54.7]), although the CIs were wide.

Both low-intensity treatment (adjusted HR 0.37 [95% CI 0.15–0.91]) and high-intensity treatment (adjusted HR 0.30 [95% CI 0.10–0.94]) were less likely to be associated with good 90-day functional outcome compared with prophylaxis only. Functional outcomes were not significantly different when comparing high- vs. low-intensity treatment (adjusted HR 1.10 [95% CI 0.31–3.88]).

Additional Outcomes

The distribution of adverse effects and head imaging studies across patients receiving any ASM treatment (combined low and high intensity) versus prophylaxis only is summarized in Supplemental Table 4. Most adverse effects, including delirium, sedation, and cardiac and gastrointestinal adverse outcomes, were more frequent in the ASM treatment group, although not significant. Patients receiving ASM treatment (combined low and high intensity) versus prophylaxis only underwent a higher number of head imaging studies ($p = 0.004$).

The median time to sustained EEG improvement was 48 h in both the prophylaxis only and ASM treatment groups. The mean time to sustained EEG improvement in the ASM treatment (combined low and high intensity) group was 62.6 h. Because the largest observed analysis time in the ASM prophylaxis group was censored, we report both restricted and extended mean times to EEG improvement. The restricted mean time for sustained improvement in the ASM prophylaxis only group was 61.2 h (largest observed analysis time was censored, and the mean time was underestimated). The extended mean time to EEG improvement (computed by exponentially extending the survival curve to zero) was 86.7 h for the ASM prophylaxis group. Only one patient in our cohort had late seizures; these occurred in the ASM continuation group at 3 months.

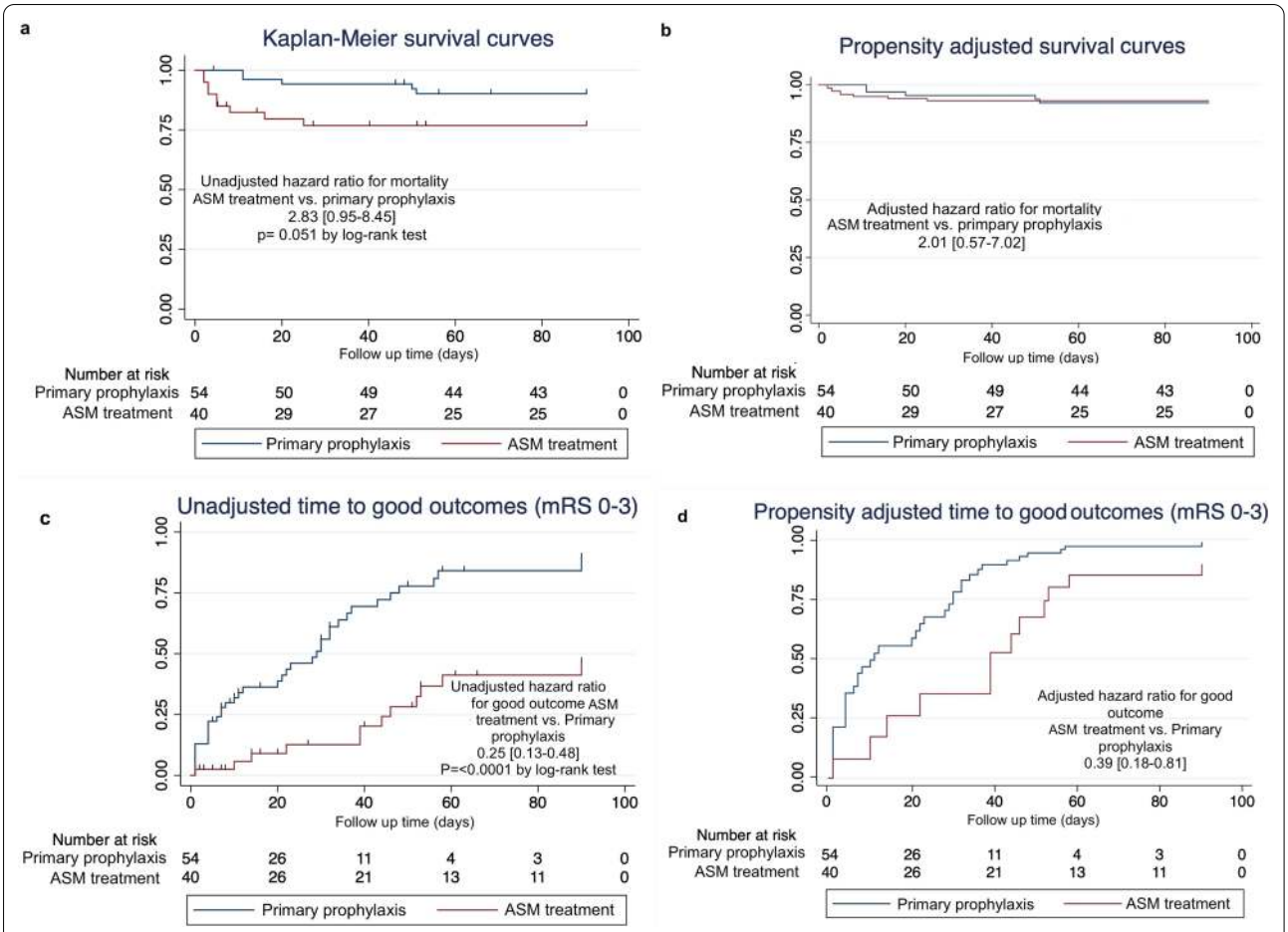

Fig. 3 90-day mortality and functional outcomes. **a** Kaplan–Meier curves for time to death comparing ASM treatment (low + high intensity) versus prophylaxis only. **b** Propensity score adjusted survival curves for time to death comparing ASM treatment (low + high intensity) versus prophylaxis only. **c** Kaplan–Meier curves for time to good functional outcome (mRS scores 0–3) comparing ASM treatment (low + high intensity) versus prophylaxis only. **d** Propensity score adjusted survival curves for time to good functional outcome (mRS scores 0–3) comparing ASM treatment (low + high intensity) versus prophylaxis only. *ASM* antiseizure medication, *mRS* modified Rankin Scale

Sensitivity Analysis

We performed an additional sensitivity analysis that included DCI in our Cox regression models. After adjustment for the propensity score and DCI, the HR for 90-day mortality was 1.82 (95% CI 0.51–5.51). After adjustment for the propensity score and DCI, ASM treatment continued to be associated with a lower likelihood of good functional outcome at 90 days (HR 0.42 [95% CI 0.20–0.88]).

Discussion

Our study adds support to the hypothesis that continuation and escalation of ASM treatments in patients with aSAH with cEEG abnormalities contributes to worse outcomes. Our data show that aggressive treatment with high-dose and multiple ASMs may be associated with increased mortality, even after adjustment for disease severity. We also found that, although low-intensity ASM treatment was not significantly associated with mortality, its association with worse functional outcomes was similar to that of high-intensity ASM treatment. Taken together, these findings suggest that the optimal approach to manage ASM treatment in patients with aSAH with epileptiform cEEG abnormalities needs to consider both the risk of harmful epileptiform abnormalities and the risk of adverse ASM effects to carefully balance risks and benefits.

In current practice, ASMs are often escalated in acutely ill patients in response to EEG findings and are often continued long-term [21, 22]. Similarly, patients with aSAH undergoing EEG monitoring are frequently treated with ASMs [2, 3]. In the absence of clear treatment guidelines, this may result in overtreatment of patients and exposure to ASM-related adverse effects. In our cohort, after propensity score adjustment, there was an increase in the hazards for worse survival in the high-intensity treatment group versus the prophylaxis only and the low-intensity groups.

Although the CIs were large, this suggests that aggressive treatment with multiple ASMs may yield net harm.

Low-intensity treatment showed a trend toward better survival; however, this effect was small and had CIs that included the null hypothesis. At the same time, low-intensity treatment was associated with worse functional outcomes. Future trials can help determine whether patients with aSAH with epileptiform abnormalities may benefit from a brief course of ASM treatment during the acute phase followed by rapid weaning to minimize adverse effects that may worsen functional outcomes.

ASM treatment (combined low and high intensity) was associated with worse functional outcomes compared with ASM prophylaxis only. Up to 80% of patients with epilepsy taking ASMs experience side effects, including cognitive slowing, gait unsteadiness, mood symptoms, headaches, and drowsiness [23–25]. These adverse effects could explain the increased likelihood of worse functional outcomes observed in patients receiving prolonged high-intensity ASM treatment. Although patients with ASM treatment had a higher frequency of adverse effects, our study was underpowered to examine significant differences in adverse effects, and larger studies will be needed to either confirm or refute our findings.

Lack of immediate EEG improvement with ASMs may result in further escalation of ASM treatment. However, EEG improvement in isolation should not be considered the only treatment end point [26]. In addition, as demonstrated in our cohort, even in patients who do not receive ASM treatment, epileptiform activity burden often decreases with time. Although clinical improvement is a more reliable target, this is often difficult to demonstrate in patients with severe aSAH who are comatose. Epileptiform activity is associated with increased brain metabolism, as demonstrated by positron emission tomography studies, which has been interpreted to imply risk for secondary brain injury [27]. In addition, epileptiform activity has been shown to be associated with decreased brain tissue oxygenation in patients with aSAH and with increased brain lactate/pyruvate ratios in patients with traumatic brain injury [28, 29]. Future studies examining such biomarkers of brain metabolism as treatment targets could provide further insight into appropriate ASM treatment strategies in this population.

New or worsening epileptiform activity in patients with aSAH is also a harbinger for DCI [7, 9]. Although DCI itself is also associated with worse outcomes, we did not include it in our regression analysis because it occurs downstream from both the development of epileptiform activity and exposure to ASM treatment. We did, however, include initial clinical presentation, imaging findings, and EEG findings in the propensity score, all of which are predictors of DCI [7, 9, 20]. In our sensitivity analysis, after adjusting for DCI, we found that ASM treatment exposure continued to have a significant association with functional outcomes. DCI pathophysiology is complex and multifactorial, including early arteriolar vasospasm, microthrombosis, spreading depolarizations, inflammatory responses, and large-vessel vasospasm [30]. Therefore ASM treatment combined with interventions geared toward increasing cerebral blood flow (e.g., induced hypertension) may serve as a more effective treatment strategy. Figure 4 provides a conceptual diagram based on our findings and our suggested interpretation of them, contrasting current practice and our hypothesized optimal treatment of cEEG epileptiform activity in patients with aSAH. We propose that the optimal treatment of patients with aSAH who are found to have epileptiform abnormalities (seizures, lateralized periodic discharges, generalized periodic discharges, and lateralized rhythmic delta activity) on cEEG is a combination of brief-duration low- to moderate-dose ASM treatment and treatments targeting cerebral perfusion and guided by biomarkers of brain metabolism. Future randomized studies are indicated to address the impact of this intervention strategy.

Limitations of our study include the retrospective nature, the small sample size, and the potential for residual confounding, which limit the ability to draw causal conclusions. This is a single-center study, limiting generalizability. Additionally, our institutional approach of primary ASM prophylaxis until the aneurysm is secured may not be generalizable. Finally, all patients with mortality were transitioned to hospice care or had life-sustaining therapies withheld. Our strict inclusion and exclusion criteria were aimed at decreasing confounding by indication; however, this came at the expense of sample size. We used propensity methodology to address confounding by indication, and as demonstrated by the shift from crude to adjusted estimates, the scores performed well in adjusting for disease severity and propensity for treatment. Nevertheless, as a retrospective analysis, our results should be taken not as proof for our proposed optimal ASM management strategy for epileptiform abnormalities but rather as supporting the need for a prospective clinical trial.

Conclusions

Our data suggest that current ASM treatment strategies in patients with aSAH may be associated with worse functional outcomes. One possible interpretation is that increased protocolized cEEG monitoring in this population leads to overtreatment and worse functional outcomes. On the other hand, there is clear evidence that epileptiform abnormalities predict DCI and are associated with worse outcomes in patients with aSAH; thus, intervening may improve outcomes [1–3, 7, 9]. Overall, it

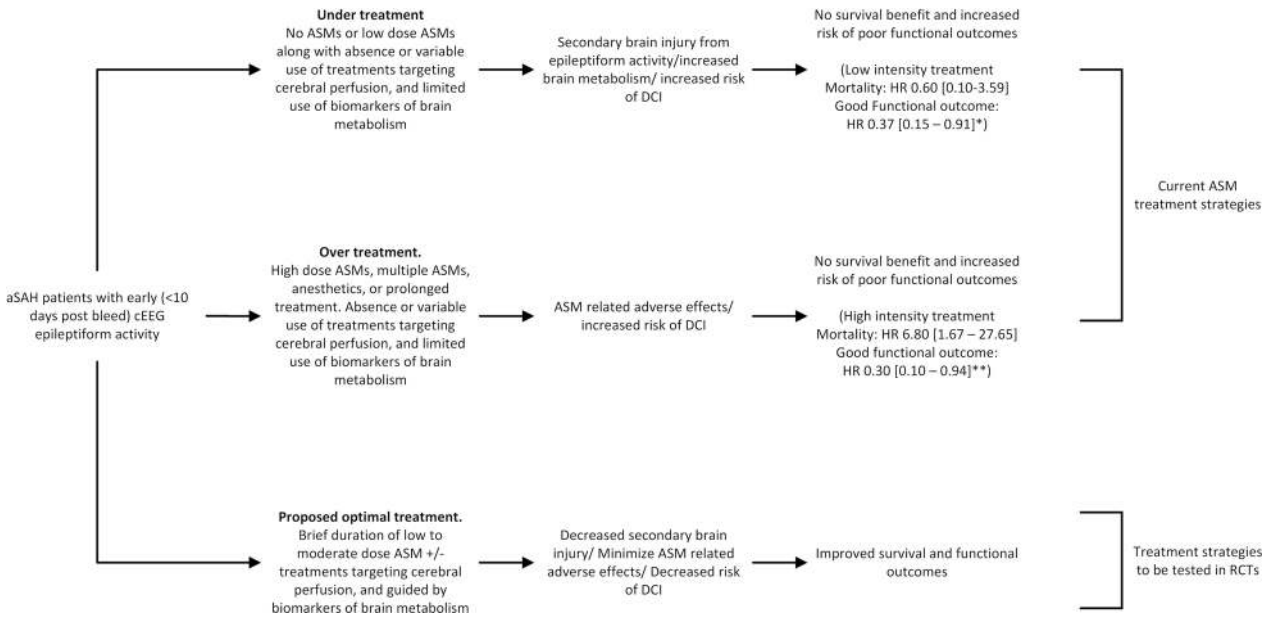

Fig. 4 Conceptual diagram contrasting ASM treatment strategies in patients with aSAH. Comparison of risks and benefits of ASM treatment at different intensities and in combination with treatment modalities aimed at improving cerebral perfusion are shown. We hypothesize that treatment of cEEG epileptiform activity with low- to moderate-dose ASMs in conjunction with treatments aimed at augmenting cerebral perfusion and guided by biomarkers of brain metabolism and oxygenation can improve survival and functional outcomes in patients with aSAH. Future randomized studies using cEEG are indicated to test this hypothesis. *Hazard ratio and confidence interval for mortality and good functional outcomes comparing low-intensity treatment with ASM prophylaxis only. **Hazard ratio and confidence interval for mortality and good functional outcomes comparing high-intensity treatment with ASM prophylaxis only. *aSAH* aneurysmal subarachnoid hemorrhage, *ASM* antiseizure medication, *cEEG* continuous electroencephalography, *DCI* delayed cerebral ischemia

is most likely that we do not yet know which cases warrant treatment, nor do we know how to match treatment intensity to the nature of the epileptiform abnormalities. Future prospective and randomized studies are needed to determine whether low- to moderate-dose treatment of epileptiform activity in the acute phase can improve survival and functional outcomes. Further work is needed to determine clear ASM treatment targets, including biomarkers for brain metabolism and cerebral blood flow. Studies using composite end points of EEG findings, clinical examination, and biomarker improvement could identify which epileptiform activity patterns warrant treatment to improve long-term outcomes. Finally, larger studies are needed to determine ASM safety and the overall risk–benefit ratio of treatment.

Supplementary Information
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Author contributions
Dr. Zafar contributed to the conception and design of the study, data collection and analysis, interpretation of data, drafting of the manuscript, and preparation of figures. Dr. Rosenthal contributed to data collection, interpretation of data, and revision of the manuscript for intellectual content. Dr. Postma contributed to data collection, interpretation of data, and revision of the manuscript for intellectual content. Dr. Sanches contributed to data collection, interpretation of data, and revision of the manuscript for intellectual content. Dr. Ayub contributed to data collection, interpretation of data, and revision of the manuscript for intellectual content. Dr. R contributed to data collection, interpretation of data, and revision of the manuscript for intellectual content. Dr. Kim contributed to data collection and interpretation and revision of the manuscript for intellectual content. Dr. Rubin contributed to data collection and interpretation and revision of the manuscript for intellectual content. Dr. Lee contributed statistical analysis, interpretation of data, and revision of the manuscript for intellectual content. Dr. Patel contributed to data collection and revision of the manuscript for intellectual content. Dr. Hsu contributed to study design, interpretation, and revision of the manuscript for intellectual content. Dr. Patorno contributed to study design, analysis, interpretation, and revision of the manuscript for intellectual content. Dr. Westover contributed to study design, analysis, interpretation of data, and revision of the manuscript for intellectual content. The final manuscript was approved by all authors.

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Declarations

Conflict of interest

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Ethical approval/informed consent

This article adheres to ethical guidelines. The study was approved by the Institutional Review Board of Mass General Brigham. Informed consent was not required for this retrospective study.

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