Review of the Utility of Prophylactic Anticonvulsant Use in Critically Ill Patients With Intracerebral Hemorrhage

Emily J. Gilmore, MD; Carolina B. Maciel, MD; Lawrence J. Hirsch, MD; Kevin N. Sheth, MD

Spontaneous atraumatic intracerebral hemorrhage (sICH) accounts for 10% to 15% of strokes a year and results in significant morbidity and mortality for survivors. The sICH-related, 30-day mortality is 30% to 50% with a significant proportion occurring in the acute phase, often in the first 48 hours, which may be a reflection of early withdrawal of life-sustaining therapy based on perceived poor neurological prognosis. Cerebrovascular disease, including sICH, is the most common cause of acute symptomatic seizures and localization-related epilepsy in adults, accounting for 3.2% to 10.7% of epilepsy. Spontaneous ICH patients typically develop seizures early after their hemorrhage, but the association between early seizures and late seizures/epilepsy remains uncertain. Our understanding of risk factors for developing seizures and epilepsy, and the role of antiseizure medications in preventing poststroke seizures and epilepsy, is based mainly on retrospective analyses. To date, there are limited data on the impact of seizures, epilepsy, and antiseizure medications on functional and cognitive outcomes in patients with sICH. The goal of this nonsystematic review is to summarize the available literature, focusing on the role of seizure prophylaxis in the immediate and long-term post-sICH periods.

Methodology
To identify key articles for inclusion, MEDLINE on the Ovid platform (through February 14, 2016) and Embase and newer (unindexed/in process) articles from PubMed were searched using the following terms or combination of terms Anticonvulsants, Seizures, Cerebral Hemorrhage, Intracranial Hemorrhage, Nontraumatic, Spontaneous and Critical Care. All identified references were then cross-referenced to select further articles for inclusion. Non-English studies and studies isolated to infants and children were excluded.

Epidemiology of sICH-Related Seizures and Epilepsy
Definitions
Seizures occur at various time points after sICH, from onset to weeks, months, and years afterward. Onset or immediate seizures occur either at ictus or within 24 hours of injury and may in fact be epileptic or could reflect convulsive syncope manifesting as loss of consciousness with posturing or jerking. Early clinical or subclinical seizures (nonconvulsive seizures [NCSz] detected on electroencephalography [EEG]), with no clinical signs other than impaired alertness) are referred to as acute symptomatic seizures; these occur in the first 7 to 14 days. Late seizures occur thereafter. Poststroke epilepsy, which previously referred to 2 unprovoked seizures >24 hours apart, at least 30 days from injury, has recently been redefined as an isolated unprovoked seizure >30 days from injury. This new definition is based on the >60% chance of seizure recurrence after a single, unprovoked, remote symptomatic seizure in patients with brain injury.

Incidence of Seizures and Status Epilepticus
The incidence of post-sICH seizures and epilepsy varies, in part, because of differences in definitions, study inclusion and exclusion criteria, and classification systems. Widespread use of continuous electrocardiography (cEEG) has increased the sensitivity of seizure capture, and consequently, more recent studies usually report a higher incidence of acute symptomatic seizures when compared with older studies. It is estimated that the overall incidence of seizures after sICH ranges from 1.7% to 31% in high-risk patients who undergo cEEG monitoring and receive seizure prophylaxis. The majority of early seizures in sICH are reported in the first 24 hours; ≤90% occur in the first 3 days. The incidence of early clinical seizures in sICH ranges from 5% to 32%, with the highest rates occurring in patients undergoing hematoma evacuation. Of all patients with clinical seizures, 4% to 60% may experience convulsive status epilepticus. Approximately 22% to 76% of patients with sICH have NCSz with ≤7% of all monitored patients experiencing nonconvulsive status epilepticus. Early seizures are thought to be directly related to neuronal dysfunction from the sICH, which is in stark contrast to the chronic changes associated with epilepsy.

Development of Epilepsy
Mechanistically, long-term gliotic changes and synaptic reorganization are the presumed culprits in the development of an
epileptogenic focus resulting in late seizures in sICH patients. Late seizures occur in 2.6% to 15.6% of sICH patients.7,11 The frequency of late seizures depends on the time of follow-up; one study estimated the risk of having a seizure within 5 years of the sICH to be 27%,20 whereas other studies have shown rates from 2.2% to 9%, even ≤10 years after injury.4,6,7,21 See Table I in the online-only Data Supplement for a summary of the most recent studies reporting acute seizures in acute stroke.5,6,13–16,18–42

Unlike in traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), there is controversy surrounding whether early or late seizures are predictive of poststroke epilepsy in sICH. Although some studies have failed to show that seizures during the acute phase are independently associated with poststroke epilepsy,7,37,38 others have conveyed a strong association.5,21,42,43 More recent literature in sICH suggests that during a protracted follow-up period, early seizures are associated with late seizures and the development of epilepsy.24,44 This is similar to TBI, where a strong association between early seizures and post-traumatic epilepsy has been shown in several cohorts.44,46 Future randomized, well-controlled studies are needed to further clarify the relationship between early seizures and epilepsy specifically in patients with sICH because this relationship, discussed above, has been shown more convincingly in other mixed populations of brain injury.

**Risk Factors for Seizures**

In mixed cohorts, the independent association varies between seizures and the stroke subtype (acute ischemic stroke, subarachnoid hemorrhage, or sICH), hemorrhage volume, stroke severity, cortical location, and younger age. These differences are largely because of heterogeneous study designs with different follow-up durations and use of antiseizure medications, as well as varying seizure identification methods and classifications. However, in multiple studies including sICH patients, proximity to the cortex remains a major factor in determining seizure risk.7,18,22,25,41,42,43 this may be related to associated SAH;52 and potentially hemorrhage volume.5,38,42,47 In a large, prospective, multicenter study, hemorrhage size was not significantly different between seizure and nonepilepsy groups, and despite cortical location being an independent predictor for seizures after sICH, it did not increase the risk for the development of epilepsy.7 In fact, hemorrhage volume >18 cc was reported to be protective against clinical seizures occurring within the first 24 hours in one prospective, single-center study, whereas lobar, but not cortical, involvement was an independent predictor of immediate seizures.20 Similarly, lobar hemorrhages have been associated with a higher risk for seizures.8,17,18,20,48 than infratentorial or subcortical hemorrhages.17,18 This evidence is not uniform, because there are studies showing a correlation of lobar hemorrhages with seizures in univariate analysis that failed to demonstrate similar associations in the multivariable model.34 Recent studies using cEEG have shown that although cortical hemorrhages are more likely to be associated with seizures, critically ill patients with subcortical and even infratentorial hemorrhages may also be at high risk of seizures.8,9,18 In a study that included a mixed cohort, occipital lesions were independently associated with higher risk of seizures at any point (relative risk of 7.68).27

In patients with pathologically diagnosed cerebral amyloid angiopathy, there is insufficient data to draw a causal association with seizures beyond the general delineation of lobar hemorrhage with or without cortical involvement. Interestingly, amyloid spells, which are transient positive or negative neurological phenomena, have been correlated with neuroimaging, especially evidence of convexity subarachnoid blood or siderosis. These spells are felt to be caused by focal seizures, cortical spreading depression, or local vasospasm, because of the focal accumulation of blood-breakdown products in the subarachnoid space and the superficial cortical layers.39

The complications of critical illness (eg, renal failure and sepsis) and many of the medications used to treat these complications (eg, antibiotics, narcotics, and antipsychotics) can lower the seizure threshold in brain injury,50 regardless of injury location, and may be risk factors for both early and late seizures in sICH (ie, provoked seizures) but have not been shown to increase the risk of subsequent epilepsy.

As has been the trend with prognosis in sICH, scores have been developed to stratify sICH patients’ risk of seizures. Recently, a post hoc analysis of the Helsinki ICH study derived the CAVE score to estimate the risk of late seizures (>7 days from ictus) in sICH and validated this instrument using the PITCH (Prognosis of Intra-Cerebral Hemorrhage) cohort based in France. The CAVE score (0–4 points) consists of cortical involvement of ICH (1 point), age <65 years (1 point), volume >10 (1 point), and early seizure within 7 days of ICH (1 point). Despite a C statistics in the derivation cohort of 0.81, its performance in the validation cohort was relatively low at 0.69.51

**Available Recommendations for Seizure Prophylaxis in sICH**

For more than a decade, the AHA stroke guidelines for seizure prophylaxis have evolved from initially extrapolating from the literature on TBI and SAH to that which reflects the emergence of sICH-specific data. The major limitation of the available retrospective analyses is that antiseizure medication use was not standardized, thus facilitating a possible bias from confounding by indication.52 The 1999 AHA guidelines stated that “prophylactic antiepileptic therapy… may be considered for 1 month and then tapered and discontinued if no seizure activity occurs during treatment, although data supporting this therapy are lacking.” In 2007, the recommendations suggested a brief period of antiepileptic therapy soon after sICH onset may reduce the risk of early seizures, particularly in patients with lobar hemorrhage. The 2010 guidelines continued to reflect the lack of data to support the early use of antiseizure medications in providing a long-term benefit to sICH patients.13,36 To date, the only class I evidence available is in support of antiseizure medications for the treatment of seizures in patients with sICH. Overall, there has been no benefit of seizure prophylaxis on neurological outcome and mortality, and studies have failed to show that seizure prophylaxis is associated with the prevention of epilepsy. However, to date, all analyses are limited by potential confounding by indication, and no large, randomized, prospective trial is available to drive decision making in sICH. See Table for a summary of the most recent guideline recommendations.53,54
Use of Prophylactic Antiseizure Medications

Despite the AHA guidelines recommending against prophylaxis, use of antiseizure medications in sICH patients varies between institutions and practitioners. See Table I in the online-only Data Supplement, where variable use of antiseizure regimens was reported across the literature. Such practices are likely extrapolated from other patient populations for whom seizure prophylaxis reduces early seizures (mainly TBI) but does not prevent late seizures or the development of epilepsy. 56,55–57 In a recent survey of stroke directors and members of the Neurocritical Care Society (n=1000), which had a 20% response rate, only 33% of respondents reported that they ever use prophylactic antiseizure medications for sICH patients. 55 Neurologists, when compared with intensivists or neurosurgeons, were significantly less likely to prescribe antiseizure medications, but when they did prescribe them, it was for significantly longer durations than the other prescribers. 55 Beyond seizure prophylaxis, directives on which medication, treatment duration, and whether treatment should differ for patients with one seizure, multiple seizures, convulsive status epilepticus, or patterns on the ictal–interictal continuum become even more challenging.

Antiseizure Medication Use and Outcome

In patients with TBI and SAH, there is mounting evidence that supports that cognitive outcomes and functional recovery may be adversely affected by antiseizure medications, particularly phenytoin. 58,59 Emerging, albeit limited, data suggest that phenytoin may be associated with worse cognitive outcomes when compared with levetiracetam in sICH patients. 36,56,60 The recent post hoc analysis of the ERICH study (Ethnic/Racial Variations of Intracerebral Hemorrhage) showed no independent association of seizure prophylaxis (predominantly levetiracetam) with unfavorable modified Rankin scores at 3 months. 56 However, these findings need to be validated in larger, prospective cohorts. Valproic acid, despite having a benign neuropsychological side effect profile, has been associated with a trend toward increased mortality after TBI, 61 but analogous studies have not been conducted after sICH.

Thus, the effects of antiseizure medications may be drug specific or even population specific, which could account for the inconsistent associations of their exposure and outcomes. Although many antiseizure medications, such as phenytoin, act to decrease neuronal excitability, they may also inhibit recovery after acute brain injury, leading to impaired cognition. This is not the case with levetiracetam, which seems to decrease neuronal irritability without affecting normal neuronal excitability. In addition, levetiracetam, with its cleaner and more linear pharmacokinetics and predominantly renal clearance, has fewer drug interactions, fewer allergies, and a more predictable therapeutic range, thus avoiding many of the problems encountered with phenytoin. 60

In the absence of randomized controlled trials of sICH patients demonstrating a robust benefit from seizure prophylaxis, routine seizure prophylaxis for all patients with sICH is not recommended. However, recognizing that seizures may increase metabolic demand, hematoma volume, and midline shift and are associated with worse outcome in sICH, 5,9 seizure prophylaxis for certain subpopulations of sICH patients may be reasonable based on known risk factors, especially if EEG monitoring is not readily available or is not closely reviewed. Patients with brain injury severe enough to explain their neurological examination (ie, proportional) are also at high risk for developing NCSz. Continuous EEG can be used as a diagnostic tool to triage the use of antiseizure medications. In cases where seizures could contribute to additional morbidity, more aggressive management may be implemented on an individual basis. If seizures are detected on cEEG, antiseizure medications aiming at seizure suppression should be initiated or escalated. The authors suggest an algorithmic approach to management based on known risk factors and the use of cEEG monitoring in sICH patients (Figure). Frequent reassessment for the need of antiseizure medication after the acute period has passed should be guided by clinical examination and the use of EEG as outlined in Figure. In addition to the algorithm, the authors have provided a table with dosing recommendations (largely based on opinion and preference rather than reliable data) for both prophylaxis and treatment (Table II in the online-only Data Supplement). The threshold for prophylaxis should perhaps be lower when cEEG...
monitoring is not available, and therefore, NCSz are likely to go undetected, particularly in comatose patients or those with elevated intracranial pressure.

Many questions still remain: should all patients with hemorrhages within 1 mm of the cortex, expanding hematomas or onset seizures, be started on antiseizure prophylaxis? If so, which agent, what dose, and for how long? If seizures persist, how aggressively should they be treated? Should it be different if a patient has early seizures or status epilepticus? Are there any reliable biomarkers suggesting which patients require antiseizure medication or which patients are likely to develop epilepsy?
Seizures and Outcome

Both seizures and the use of antiseizure medications have been suggested to worsen outcome after sICH. A few studies have explored the relationship between early antiseizure medication use and outcome, albeit with mixed results. Only one of these studies applied EEG monitoring and accounted for NCSzs, which are the majority of seizures after sICH. Two Intensive Care Unit-based series published in 2003 and 2007 of sICH patients who underwent cEEG showed an independent association between electrographic seizures and poor outcome. Seizures (most of which were nonconvulsive) were not only independently associated with early sICH expansion but also progressive midline shift and an associated trend toward worse functional outcomes. However, based on these limited data implicating causality, it remains uncertain in sICH whether seizures are simply a proxy for the extent of brain injury or independently cause additional harm. Although there is extensive circumstantial and theoretical evidence that seizures are harmful for the acutely injured brain, no prospective randomized trial has been performed to see whether treatment can improve neurological outcome or any other long-term outcome measure.

Additionally, studies have failed to convincingly show that seizures are associated with mortality in sICH. A post hoc analysis of the FUTURE cohort (Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation study) demonstrated that functional outcomes were adversely affected by poststroke epilepsy in the ischemic stroke subset, but not in the sICH subpopulation. In addition, poststroke epilepsy has been associated with mortality in young adults (18–50 years of age) with acute ischemic stroke but remains an open question in sICH. There is an ongoing multicenter registry (ODYSSEY) that was designed to determine long-term prognosis after acute stroke, including sICH, in patients aged 18 to 49, and hopefully will clarify the association between poststroke epilepsy and outcomes, including cognitive impairment.

Further studies investigating the impact of late seizures or epilepsy after sICH on functional outcome, neurocognitive recovery, quality of life, and psychiatric sequelae (ie, depression, anxiety, post-traumatic stress disorder) are needed to answer many of the remaining questions.

Beyond Seizures: EEG Patterns of Undetermined Significance

In addition to seizures, because more critically ill sICH patients undergo EEG monitoring, periodic and rhythmic EEG patterns will be detected, because such patterns are seen in almost half of critically ill patients undergoing cEEG. Although clearly associated with an increased risk of seizures, it remains unclear whether such patterns may themselves be as harmful as seizures and warrant aggressive treatment beyond seizure prophylaxis. Some studies using cEEG report on such patterns and their association with seizures in sICH. In one study, periodic epileptiform discharges were recorded in 17% of patients (periodic lateralized epileptiform discharges 13%, generalized periodic epileptiform discharges 6%, and bilaterally independent periodic lateralized epileptiform discharges 1%) and were associated with electrographic seizures (59% versus 9%).

Among other EEG findings, periodic lateralized epileptiform discharges (now known as LPDs) and focal stimulus-induced rhythmic, periodic, or ictal discharges have been found to be independently associated with poor outcome. However, the temporal relationship between seizures and EEG patterns is not clear in the current literature. Thus, on the one hand, it is not known whether such patterns are in fact as harmful as seizures and on the other hand, if such patterns, when left untreated, will invariably precipitate the emergence of more definite seizures. Regardless, the implication is that there may be a window of intervention that could ultimately impact outcome. The fact that rhythmic or periodic patterns are highly associated with seizures and may in fact be ictal or harmful becomes relevant in light of a recent publication in SAH patients that suggested having even one seizure is associated with worse functional outcomes at 3 months from injury. A recent study, which included patients with both electrographic status epilepticus and EEG patterns that do not qualify as electrographic status epilepticus, reported that fluorodeoxyglucose (FDG)-positron emission tomography (PET) hypermetabolism was common across the cohort of patients with varying neurological diagnoses including sICH. Future studies aimed at elucidating clinically relevant and useful biomarkers to discern which EEG patterns are harmful, independent of disease severity, will hopefully help to answer questions about these uncertain EEG patterns.

Future Directions

Our knowledge of seizures as a clinical feature of sICH is mostly based on retrospective cohort studies. Thus, our understanding of prevalence, frequency, temporal distribution, and characteristics of seizures, as well as factors predisposing to seizures and their prognostic significance for short-term mortality and long-term risk of epilepsy, is limited. Additionally, early seizures likely have different predisposing factors than delayed post-ICH seizures (ie, epilepsy). Many predisposing factors may coalesce to synergistically cause seizures. The single, randomized, double-blinded, placebo-controlled trial of antiseizure medications for seizure prevention in sICH was limited by a small sample size (n=72), treatment bias, and the use of clinically reported events without the use of cEEG. Currently, there is insufficient evidence to support the routine use of antiseizure medications for the prevention of seizures after sICH, and this is consistent with published guidelines. Although the SPICH study (Seizure Prophylaxis Following Intracerebral Hemorrhage), which is currently underway, may show promise clarifying whether short-term sodium valproate has an effect on seizure incidence as well as survival and neurological outcome in sICH, the very low dose (500 mg PO daily or 400 mg IV daily), relatively small sample size, and single-center design may leave many questions unanswered. Studies assessing the efficacy and tolerability, optimal timing, duration, and the weaning process of antiseizure medications across the spectrum of sICH-related seizures are needed. Such studies will need to recruit large numbers of patients and consider clinically meaningful outcomes. Ideally, future studies should be double blind, compare multiple antiseizure medications and different dosing to placebo, use cEEG and include long-term follow-up aimed at addressing the development of epilepsy, seizure-free periods, medication compliance, and functional and cognitive outcomes.
Although there have been several recent acute sICH trials—ATACH, ERICH, MISTIE, CLEAR-IHV, STICH, INTERACT, and iDEF—all addressing secondary injury, there are no current interventional studies assessing seizures, antiepileptic medication-prescribing patterns, or epilepsy and related outcomes. There are data to suggest that seizures are harmful: they increase edema, metabolic rate, and midline shift and are independently associated with worse outcome. Thus, only a prospective randomized clinical trial, perhaps building on the infrastructure of either ongoing or future sICH trials, will be able to more definitively answer whether seizure prophylaxis in the acute or longer term setting is beneficial or not. A large prospective randomized trial of seizure prophylaxis, which attacks these questions is urgently needed.

Currently, there is insufficient evidence to support the routine use of antiepileptic drugs (AEDs) for the primary or secondary.

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References


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SUPPLEMENTAL MATERIAL
Supplemental Table I. Summary of most recent acute stroke studies including spontaneous nontraumatic intracerebral hemorrhage reporting incidence of acute seizures and/or post-stroke epilepsy.

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Type of study</th>
<th>Sample Size (# of patients in total, and according to stroke subtype)</th>
<th>Anti-Seizure Medication</th>
<th>EEG Obtained</th>
<th>Early-Onset Seizures (% overall, and according to stroke subtype)</th>
<th>Late-Onset Seizures (% overall, and according to stroke subtype)</th>
<th>Overall Incidence of Seizures (% overall, and according to stroke subtype)</th>
<th>Seizure Type (% of patients who had seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berges et al¹, 2000</td>
<td>Retrospective Single center</td>
<td>3,205 2,742 AIS 463 sICH</td>
<td>NA</td>
<td>Y</td>
<td>1.8% † 1.1% AIS 5.8% sICH</td>
<td>3.2% † 3.1% AIS 3.4% sICH</td>
<td>4.96%</td>
<td>35.8% PSz 27.6% SGSz 36.5% GSz 19.4% SE §</td>
</tr>
<tr>
<td>Bladin et al², 2000</td>
<td>Prospective Multicenter</td>
<td>1,897 1,632 AIS 2,65 sICH</td>
<td>NA</td>
<td>NA</td>
<td>7.3% † 4.8% AIS 7.9% sICH</td>
<td>1.4% † 3.8% AIS 2.6% sICH</td>
<td>8.9%</td>
<td>52% PSz +SGSz</td>
</tr>
<tr>
<td>Labovitz et al³, 2001</td>
<td>Prospective Single center</td>
<td>904 704 AIS 150 sICH 50 SAH</td>
<td>NA</td>
<td>NA</td>
<td>4.1% † 3.1% AIS 7.3% sICH 8% SAH</td>
<td>NA</td>
<td>NA</td>
<td>59.5% PSz 24.3% GSz 16.2% U 27% SE §</td>
</tr>
<tr>
<td>Passero et al⁴, 2002</td>
<td>Prospective Single center</td>
<td>761 sICH</td>
<td>Variable regimen (PB in 65.1% after onset; details NA)</td>
<td>NA</td>
<td>3.2% **</td>
<td>NA</td>
<td>7.5%</td>
<td>28% PSz 52% GSz 20% SE §</td>
</tr>
<tr>
<td>Vespa et al⁵, 2003</td>
<td>Prospective Single center</td>
<td>109 46 AIS 63 sICH</td>
<td>Primary prophylaxis +/- treatment (PHT) † †</td>
<td>Y ‡ ‡</td>
<td>NA</td>
<td>NA</td>
<td>19.2% 6% AIS 28% sICH</td>
<td>76% NCSz 19% CSz ‡ ‡ 5% CESz</td>
</tr>
<tr>
<td>Benbir et al⁶, 2006</td>
<td>Prospective Single center</td>
<td>1,428 1,327 AIS 86 sICH 15 CVT</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.6% ‡ ‡ 2.7% AIS 12.8% sICH 26.6% CVT</td>
<td>NA</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>ROI</td>
<td>n/Type</td>
<td>Prophylaxis</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Other Prognosis</td>
<td></td>
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<tr>
<td>Claassen et al(^7), 2007</td>
<td>Retrospective</td>
<td>Single center</td>
<td>102 sICH</td>
<td>Variable regimen(|)</td>
<td>Y  (#)</td>
<td>NA</td>
<td>31% (***)</td>
<td>59% CSz 3.1% CESz 53% NCSz 39% NCSE (|||)</td>
</tr>
<tr>
<td>Alberti et al(^8), 2008</td>
<td>Prospective</td>
<td>Single center</td>
<td>638</td>
<td>NA</td>
<td>4.8% (|)</td>
<td>4.8% AIS 5.2% sICH</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Szaflarski et al(^9), 2008</td>
<td>Retrospective</td>
<td>Population based</td>
<td>6,044</td>
<td>NA</td>
<td>3.1% (|||)</td>
<td>2.4% AIS 7.9% sICH 10.1% SAH</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Andaluz et al(^10), 2009</td>
<td>Retrospective</td>
<td>NIS Database</td>
<td>905,152 sICH</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>19.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Garrett et al(^11), 2009</td>
<td>Retrospective</td>
<td>Single center</td>
<td>98 sICH/OR</td>
<td>Variable regimen (|)</td>
<td>Y  (||)</td>
<td>31.5% (|)</td>
<td>10.2% (|)</td>
<td>41.8% 29.6% CESz</td>
</tr>
<tr>
<td>Messe et al(^12), 2009</td>
<td>Prospective</td>
<td>Multicenter</td>
<td>295 sICH</td>
<td>Variable regimen (|)</td>
<td>NA</td>
<td>NA</td>
<td>1.7%</td>
<td>NA</td>
</tr>
<tr>
<td>Naidech et al(^13), 2009</td>
<td>Prospective</td>
<td>Single center</td>
<td>98 sICH</td>
<td>Variable regimen (|)</td>
<td>Y  (||)</td>
<td>NA</td>
<td>7.1%</td>
<td>0% SE</td>
</tr>
<tr>
<td>Yang et al(^14), 2009</td>
<td>Retrospective</td>
<td>Single center</td>
<td>243 sICH</td>
<td>No primary prophylaxis</td>
<td>NA</td>
<td>3.7% (|||)</td>
<td>4.5% (|)</td>
<td>8.2% 0% SE</td>
</tr>
<tr>
<td>Burneo et al(^15), 2010</td>
<td>Prospective</td>
<td>Multicenter</td>
<td>5027 AIS 4083 AIS 939 ICH 5 U</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.7% 2.0% AIS 5.7% sICH</td>
<td>NA</td>
</tr>
<tr>
<td>Beghi et al(^16), 2011</td>
<td>Prospective</td>
<td>Multicenter</td>
<td>714 609 AIS 105 sICH</td>
<td>Variable regimen (|)</td>
<td>Y</td>
<td>6.3% (|)</td>
<td>4.6% AIS 16.2% sICH</td>
<td>NA</td>
</tr>
</tbody>
</table>
| Study                     | Design     | Setting           | Total patients | sICH patients | Primary prophylaxis | Y Y Y Y
<table>
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<tbody>
<tr>
<td>De Herdt et al(^{17}), 2011</td>
<td>Prospective</td>
<td>Single center</td>
<td>522</td>
<td>14%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gilad et al(^{18}), 2011</td>
<td>Prospective</td>
<td>Single center</td>
<td>72</td>
<td>13.8%</td>
<td>Y</td>
<td>20.8%</td>
</tr>
<tr>
<td>Mecarelli et al(^{19}), 2011</td>
<td>Prospective</td>
<td>Single center</td>
<td>232</td>
<td>6.5%</td>
<td>Y****</td>
<td>NA</td>
</tr>
<tr>
<td>Goswami et al(^{20}), 2012</td>
<td>Prospective</td>
<td>Single center</td>
<td>441</td>
<td>17.9%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Okuda et al(^{21}), 2012</td>
<td>Retrospective</td>
<td>Single center</td>
<td>448</td>
<td>4.9%</td>
<td>NA</td>
<td>5.1%</td>
</tr>
<tr>
<td>Woo et al(^{22}), 2012</td>
<td>Retrospective</td>
<td>Single center</td>
<td>263</td>
<td>3.4%</td>
<td>NA</td>
<td>4.9%</td>
</tr>
<tr>
<td>Arntz et al(^{23}), 2013</td>
<td>Prospective</td>
<td>Single center</td>
<td>697</td>
<td>3.6%</td>
<td>NA</td>
<td>11.3%</td>
</tr>
<tr>
<td>Conrad et al(^{24}), 2013</td>
<td>Retrospective</td>
<td>Single center</td>
<td>421</td>
<td>5.4%</td>
<td>NA</td>
<td>11.6%</td>
</tr>
<tr>
<td>Rossi et al(^{25}), 2013</td>
<td>Prospective</td>
<td>Single center</td>
<td>325</td>
<td>15.7%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| Wang et al\(^{26}\), 2013   | Prospective |                | 2094           | 5.9%            | Y+++              | 11.1%           | 51% PSz
|                           |            |                  |                |                   |                     | 43% GSz
|                           |            |                  |                |                   |                     | 4% SE
|                           |            |                  |                |                   |                     | 1% U
|                           |            |                  |                |                   |                     | 53.3% SGSz
|                           |            |                  |                |                   |                     | 46.6% PSz
|                           |            |                  |                |                   |                     | 60% CSE
|                           |            |                  |                |                   |                     | 6.6% NCSE
|                           |            |                  |                |                   |                     | 4.5% SE
|                           |            |                  |                |                   |                     | 50% PSz
|                           |            |                  |                |                   |                     | 45% SGSz or GSz
|                           |            |                  |                |                   |                     | 26.6% SGSz
|                           |            |                  |                |                   |                     | 36.7% PSz
|                           |            |                  |                |                   |                     | 31.6% GSz
|                           |            |                  |                |                   |                     | 5.1% U
|                           |            |                  |                |                   |                     | 38.8% PSz
|                           |            |                  |                |                   |                     | 57.1% SGSz
|                           |            |                  |                |                   |                     | 4.1% U
|                           |            |                  |                |                   |                     | 16.7% SE
|                           |            |                  |                |                   |                     | 65.5% PSz
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Center</th>
<th>Total Patients</th>
<th>AIS Cases</th>
<th>sICH Cases</th>
<th>SAH Cases</th>
<th>Other Events</th>
<th>Y = 4%</th>
<th>NA</th>
<th>NA</th>
<th>SE = 22.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Multicenter</td>
<td>947</td>
<td>904</td>
<td>243</td>
<td>5.3% AIS</td>
<td>5.2% sICH</td>
<td>10.7% SAH</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>34.5% SGSz</td>
</tr>
<tr>
<td>Guth et al27, 2014</td>
<td>Prospective Single center</td>
<td>234</td>
<td>Variable regimen (60% LEV primary prophylaxis)</td>
<td>Y††††</td>
<td>4% ⌂∥∥∥∥</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td>22.2% SE∥∥∥∥</td>
<td></td>
</tr>
<tr>
<td>Serafini et al28, 2015</td>
<td>Prospective Multicenter</td>
<td>782</td>
<td>NA</td>
<td>NA</td>
<td>5.1%</td>
<td>2.8% AIS</td>
<td>2.8% AIS</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al29, 2015</td>
<td>Prospective Multicenter</td>
<td>3216</td>
<td>NA</td>
<td>NA</td>
<td>4.3%</td>
<td>2.3%</td>
<td>6.6%</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neshige et al30, 2015</td>
<td>Retrospective Single center</td>
<td>1920</td>
<td>Variable regimen (details NA)</td>
<td>NA</td>
<td>4.3%</td>
<td>2.3%</td>
<td>6.6%</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruning et al31, 2016</td>
<td>Prospective Single center</td>
<td>484</td>
<td>Variable regimen (LTG, VPA, CBM, LEV, PGB, CLO, PB)</td>
<td>Y</td>
<td>10.7%</td>
<td>NA</td>
<td>NA</td>
<td>57.7% PSz</td>
<td>32.7% GSz</td>
<td>5.7% SGSz</td>
<td></td>
</tr>
<tr>
<td>Hundoz et al32, 2016</td>
<td>Retrospective Single center</td>
<td>1073</td>
<td>NA</td>
<td>NA</td>
<td>4.1%</td>
<td>4.1% AIS</td>
<td>4.0% sICH</td>
<td>NA</td>
<td>NA</td>
<td>3.8% U</td>
<td></td>
</tr>
</tbody>
</table>

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* Studies have different inclusion and exclusion criteria. TIAs were frequently included in the AIS cohort. Ischemic stroke with hemorrhagic transformation were also included in the AIS cohort. sICH included atrumatic parenchymal hemorrhages, often times those secondary to small vessel disease such as hypertension and cerebral amyloid angiopathy, however, some studies included cerebral venous infarct in this category as well. Patients with prior history of seizures, those who did not survive initial week of hospitalization, and those with infratentorial strokes were often, but not always, excluded from analysis in most studies.

† Early-onset seizures defined as occurring within initial 14 days after stroke.

‡ Late-onset seizures defined as occurring after 2 weeks following stroke.

§ Authors do not report data on subclinical seizures.
Early seizure defined as occurring within initial 7 days after stroke and late seizure defined as occurring any time during follow up period after 7 days from stroke onset. The original paper may have used a different terminology.

All reported status epilepticus cases were convulsive in nature.

Early seizures defined as those occurring within 30 days but not initial 24 hours of stroke onset.

Prophylactic phenytoin administration aimed at maintaining levels of 14-18 mg/dL was the primary prophylaxis used. Additionally, boluses of phenytoin, lorazepam and phenobarbital were used when seizures developed despite primary prophylaxis.

All consecutive stroke patients were continuously monitored beginning at the earliest opportunity after the admission to the ICU. Patients that exhibit clinical seizures only (CSz) did not experience recurrent seizures after they were monitored with EEG.

Reported post-stroke epilepsy defined as ≥ 2 unprovoked epileptic seizures occurring at least 1 week after the stroke.

Patients with lobar hemorrhages and depressed level of consciousness were loaded with phenytoin 20mg/kg and kept on maintenance for therapeutic levels as primary prophylaxis. Secondary prophylaxis was left at the discretion of treating clinician.

This cohort represents 13% of all sICH admissions during the study time frame. EEG monitoring indication is not available, but 76% of monitored patients had altered mental status at time of initiation of monitoring.

Seizures at any time from onset of hemorrhage to hospital discharge.

This percentage refers to the number of patients with electrographic seizure detected on continuous monitoring. Nonconvulsive status epilepticus had an incidence of 7% of all monitored patients (representing the entire cohort of this study) and 22% of all patients that exhibit any seizure activity (including those that had clinical seizures prior to being monitored).

Early-onset seizures defined as occurring within 24 hours of hemorrhage.

Patients with fluctuating exam, depressed level of consciousness, and in whom the clinician suspected seizures were monitored with continuous EEG.

In this table, we included both immediate seizures (associated with ictus bleeding) and early seizures defined by original paper as those occurring within 14 days of hemorrhage.

Randomization to valproic acid primary prophylaxis targeting levels of 50 – 100 µg/dL or placebo for one month. Secondary seizure prophylaxis was maintained to all patients.

EEG was initiated within 24 hours of admission in all patients.

EEG was initiated within 24-48 hours of admission in all patients.

Continuous EEG monitoring for ≥48 hours in patients with a depressed mental status.

Early-onset seizures defined as occurring within 72 hours of stroke onset.

There were 2 cases of status epilepticus in this cohort, which represented 22.2% of patients who experienced seizure at any point during the follow up.

One patient had convulsive status epilepticus and also exhibited NCSE when monitored. Another patient had NCSE.

AIS – acute ischemic stroke
CBM – carbamazepine
CESz – clinical and electrographic seizure
CLO – clobazam
CSz – clinical seizures only prior to being monitored on EEG
CSE – convulsive status epilepticus
CVT – cerebral venous thrombosis
EEG – electroencephalography
fosPHT – fosphenytoin
GBP – gabapentin
GSz – generalized seizure
ICU – intensive care unit
LEV – levetiracetam
LTG – lamotrigine
NA – either non applicable or data not available from original paper
NCz – nonconvulsive seizures
NCSE – nonconvulsive status epilepticus
NIS – nationwide inpatient sample
OR – patients requiring surgical evacuation of hemATOMA
OXC – oxcarbazepine
PB – phenobarbital
PGB – pregabalin
PHT – phenytoin
PRM – primidone
PSz – partial seizure
SAH – subarachnoid hemorrhage
SE – status epilepticus
SGSz – partial seizure with secondary generalization
sICH – spontaneous nontraumatic intracerebral hemorrhage
TIA – transient ischemic attack
TPM – topiramate
U – unclear semiology
VPA – valproic acid
Bibliography


31. Bruning T, Awwad S, Al-Khaled M. Do early seizures indicate survival of patients with nontraumatic intracerebral hemorrhage? *Cerebrovascular diseases (Basel, Switzerland)*. 2016;41:68-73

Supplemental Table II. Anti-seizure medications and recommended doses for prophylaxis or treatment of intermittent seizures (not for status epilepticus)

<table>
<thead>
<tr>
<th></th>
<th>Loading dose</th>
<th>Prophylaxis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>20-40 mg/kg in &gt;15 min</td>
<td>500mg QID (adjust level to 60-100µg/mL)</td>
<td>Extra 15 mg/kg in 15 min pm then 1000mg TID (adjust to level of 75-125 µg/mL)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1500-4000 mg in &gt;15 min</td>
<td>500mg-750 mg BID</td>
<td>Extra 1000mg in 15min pm, then 750 TID; increase pm to max 1000 QID</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>200-300 mg in &gt;15 min</td>
<td>100mg-200 mg BID</td>
<td>Extra 100 mg in 15 min then 100 mg TID; increase pm to max 200 TID</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>15-18 mg/kg in &gt;30 min</td>
<td>100 TID (adjust total level 10-20µg/mL or free level to 1.0-2.5µg/mL)</td>
<td>Extra 5 mg/kg in 30 min pm, then 100 QID (adjust total level to 15-25µg/mL or free level 1.5-3.0µg/mL)</td>
</tr>
</tbody>
</table>