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NCS GUIDELINES

Guidelines for Seizure Prophylaxis in Patients Hospitalized with Nontraumatic Intracerebral Hemorrhage: A Clinical Practice Guideline for Health Care Professionals from the Neurocritical Care Society

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Abstract

Background: There is practice heterogeneity in the use, type, and duration of prophylactic antiseizure medications (ASM) in patients hospitalized with acute nontraumatic intracerebral hemorrhage (ICH).

Methods: We conducted a systematic review and meta-analysis assessing ASM primary prophylaxis in adults hospitalized with acute nontraumatic ICH. The following population, intervention, comparison, and outcome (PICO) questions were assessed: (1) Should ASM versus no ASM be used in patients with acute ICH with no history of clinical or electrographic seizures? (2) If an ASM is used, should levetiracetam (LEV) or phenytoin/fosphenytoin (PHT/fPHT) be preferentially used? and (3) If an ASM is used, should a long (> 7 days) versus short (≤ 7 days) duration of prophylaxis be used? The main outcomes assessed were early seizure (≤ 14 days), late seizures (> 14 days), adverse events, mortality, and functional and cognitive outcomes. We used Grading of Recommendations Assessment, Development, and Evaluation methodology to generate recommendations.

Results: The initial literature search yielded 1,988 articles, and 15 formed the basis of the recommendations. PICO 1: although there was no significant impact of ASM on the outcomes of early or late seizure or mortality, meta-analyses demonstrated increased adverse events and higher relative risk of poor functional outcomes at 90 days with prophylactic ASM use. PICO 2: we did not detect any significant positive or negative effect of PHT/fPHT compared to LEV for early seizures or adverse events, although point estimates tended to favor LEV. PICO 3: based on one decision analysis, quality-adjusted life-years were increased with a shorter duration of ASM prophylaxis.

Conclusions: We suggest avoidance of prophylactic ASM in hospitalized adult patients with acute nontraumatic ICH (weak recommendation, very low quality of evidence). If used, we suggest LEV over PHT/fPHT (weak recommendation, very low quality of evidence) for a short duration (≤ 7 days; weak recommendation, very low quality of evidence).

Keywords: Intracerebral hemorrhage, Seizure, Prophylaxis, Prophylactic, Prevention, Antiseizure medication, Antiepileptic medication, Phenytoin, Fosphenytoin, Dilantin, Levetiracetam, Keppra, Outcome, EEG, Epilepsy, Guideline, Recommendation

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Introduction

The incidence of seizure following nontraumatic intracerebral hemorrhage (ICH) is estimated to range from 6 to 31% during the initial days after hemorrhage onset [1–4], with the majority of seizures being electrographic only (nonconvulsive) [3]. Although seizures are more common with lobar ICH, a significant proportion (up to 21%) of patients with deep or subcortical hemorrhages have been reported to have seizures during the first 72 h after ICH onset [2]. Patients with ICH who undergo surgical clot evacuation have even higher rates of seizures, with an incidence of clinical or electrographic seizure as high as 42% during hospitalization [5]. Despite the high rates of post-ICH seizure, the use of prophylactic antiseizure medication (ASM) following nontraumatic ICH has been found to vary widely depending on individual patient characteristics [6] and physician specialty [7, 8]. Furthermore, the type of ASM, duration of use, use of electroencephalogram (EEG), and drug level monitoring are highly heterogeneous among practitioners [7, 8]. The American Heart Association guidelines for the management of patients with spontaneous ICH recommend against prophylactic ASM because of the lack of benefit regarding functional outcomes, long-term seizure control, or mortality [9]. However, these guidelines were not primarily focused on seizure prophylaxis, and no meta-analysis or systematic review of the literature was conducted. Hence, this guideline addresses points not previously addressed by other sources.

Given the paradox of high rates of subtle and electrographic seizures following ICH and guidelines that recommend against seizure prophylaxis [9], the Neurocritical Care Society undertook a systematic review and meta-analysis of the literature following Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [10, 11] to generate evidence-based guidelines for the use of seizure prophylaxis following acute nontraumatic ICH. These guidelines are part of a series of articles addressing ASM prophylaxis in neurocritically ill patients, including those with traumatic brain injury, spontaneous subarachnoid hemorrhage, and supratentorial neurosurgery. The topic of ASM prophylaxis in patients with ICH who undergo a neurosurgical procedure will be covered in the supratentorial neurosurgery guideline.

The main questions we aimed to address were as follows: (1) Should prophylactic ASM versus no ASM be used in patients with acute nontraumatic ICH with no history of clinical or electrographic seizures? (2) If an ASM is used, should levetiracetam (LEV) or phenytoin/fosphenytoin (PHT/fPHT) be preferentially prescribed? and (3) If an ASM is used, what is the appropriate duration of prophylaxis?

Methods

This guideline was developed in accordance with GRADE methodology [11, 12], and both panel co-chairs (JAF and SR) completed GRADE workshop training [10].

Panel Composition

The Seizure Prophylaxis Guideline Panel was formed in October 2019 and consists of nine members, including pharmacists, physicians, and nurses, with subspecialty experience in neurocritical care, neurosurgery, epilepsy, and trauma. In addition, a GRADE statistician (YY) performed statistical analyses. The panel consisted of six women and four men of diverse racial and ethnic backgrounds (Asian, South Asian, White, and Hispanic).

Disclosure and Management of Potential Conflicts of Interest

All panel members were required to comply with standard conflict of interest and commercial relationship disclosures, including review of any financial, intellectual, or other relationships that may be construed as a possible conflict of interest. The chairs of the Neurocritical Care Society Guideline Committee, which oversees the Seizure Prophylaxis Guideline Panel, were responsible for vetting any potential conflicts of interest. Disclosures that were unrelated to the content of this article are listed in the Conflicts of interest section. All members of the Seizure Prophylaxis Guideline Panel were determined to be free of conflicts of interest.

PICO Generation

The population, intervention, comparison, and outcome (PICO) [13] questions were as follows: (1) Should ASM versus no ASM be used in patients with acute nontraumatic ICH with no history of clinical or electrographic seizures? (2) If an ASM is used, should LEV or PHT/fPHT be preferentially used in patients with nontraumatic ICH with no history of clinical or electrographic seizures? and (3) If an ASM is used, should a long (>7 days) versus short (≤7 days) duration of prophylaxis be used for patients with nontraumatic ICH and no history of clinical or electrographic seizures? The comparison of LEV versus PHT/fPHT was selected based on the number of articles directly evaluating these ASMs. Although newer ASMs (e.g., lacosamide, brivaracetam) may be preferred in certain circumstances because of the behavioral side effects of LEV [14], there was a paucity of data comparing these ASMs to LEV or PHT, making a systematic review and meta-analysis difficult.

Outcomes were ranked in order of importance as "critical" (indicating the highest level of importance), which included early seizure (either clinical or electrographic) occurring within 14 days of ICH, late seizure

(either clinical or electrographic) occurring > 14 days from ICH, and adverse events associated with ASM use. A 14-day threshold for early versus late seizure was selected because some studies defined early seizure as within 7 days, others defined it as within 14 days, and still others defined it as a seizure occurring during hospitalization. Because the threshold of 7 or 14 days is not biologically driven, we chose 14 days to be inclusive of the most studies. Studies that identified seizures during hospitalization were grouped with the early seizure (< 14 day) category. A second level of outcomes ranked as "important" included mortality, functional disability (e.g., modified Rankin scale [mRS] scores [15], Glasgow Outcome Scale) and cognitive outcomes. Not enough data were available to assess cost or quality of life outcomes.

Study Population

This guideline pertains to adult patients hospitalized with acute, spontaneous nontraumatic ICH who do not have a history of seizure (clinical or electrographic) or ASM use (for any indication) prior to the index ICH. We included patients with lobar ICH, deep/subcortical ICH, pure intraventricular hemorrhage (IVH), and multicompartmental hemorrhages if the primary hemorrhage was intracerebral who presented to the hospital within one week of hemorrhage onset. We included studies with mixed ICH regions, including supratentorial and infratentorial locations. Studies including patients with ICH due to trauma or aneurysm rupture were excluded. Additional guidelines for ASM prophylaxis focused on patients with moderate-severe traumatic brain injury, spontaneous subarachnoid hemorrhage, and supratentorial neurosurgery are published separately.

Inclusion and Exclusion Criteria

Studies could be included if the following criteria were met: the article addressed prophylactic ASM use, the study included an adult population (aged ≥ 18 years) hospitalized with ICH, and data were available on the primary outcomes of interest (early seizure, late seizure, adverse events, mortality, functional outcomes, or cognitive outcomes). Articles were excluded if they involved patients with a history of seizure, epilepsy, or ASM use prior to ICH (for any indication); were not published in English; were nonhuman studies; were case series with < 10 patients; evaluated a pediatric population; or did not assess an outcome of interest. We excluded gray literature such as abstracts, conference proceedings, and non-peer-reviewed articles, as well as review articles and meta-analyses.

Search Strategy

A search of articles was conducted by an independent medical librarian from January 1, 1946, through July 10, 2020, using PubMed, Medline, Embase, Emcare, and Cochrane databases (Supplemental Table 1). Additional literature searches were performed by panel members between July 10, 2020, and November 1, 2022, to capture more recently published articles. Search terms included the following: "seizure," "antiepileptic medication," "antiseizure medication," "levetiracetam," "Keppra," "lacosamide," "Vimpat," "phenytoin," "Dilantin," "fosphenytoin," "Cerebyx," "valproic acid," "Depakote," "carbamazepine," "lamotrigine," "prophylaxis," "prevention," "prophylactic," "intracerebral hemorrhage," "ICH," "intraparenchymal hemorrhage," "intracranial hemorrhage," "mortality," "death," "functional outcome," "function," "modified Rankin," "Glasgow Outcome score," "cognition," "cognitive," "disability," "activities of daily living," "outcome," "adverse events," and "side effects." Reference lists of published articles, review articles, and meta-analyses were also screened to identify additional articles.

Study Screening and Data Collection

Two reviewers independently screened each article title and abstract to determine inclusion eligibility. Full text screening was performed in articles that passed the initial level of review. Screening was performed using DistillerSR software (Ottawa, Ontario, Canada), and all conflicts were adjudicated between reviewers prior to study inclusion. Data were extracted into a standardized tool and classified as randomized controlled trials (RCTs) versus nonrandomized studies, which could be observational studies using retrospective, prospective, cross-sectional, or case series design.

Risk of Bias and Certainty of Evidence Evaluation

Risk of bias tools were selected based on recommendations from GRADE and the types of articles evaluated. Bias in randomized trials was assessed using the Cochrane Risk of Bias 2 (RoB-2) [16] tool, and bias in nonrandomized studies was assessed using the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool [17]. Final risk of bias scores were adjudicated with the study group. RoB-2 scoring specifically addresses randomization bias, bias related to deviation from intended interventions, bias due to missing outcome data, bias in measurement of outcome, and bias in selection of the reported result. The ROBINS-I assessment accounts for bias in confounding, bias in patient selection, bias in classification of interventions, bias related to deviations from intended

Table 1 Summary of recommendations for seizure prophylaxis in patients with acute nontraumatic ICH

	Recommendation	Level of recommendation, quality (certainty) of evidence	Justification
PICO 1	Should ASM versus no ASM be used in patients hospitalized for acute nontraumatic ICH with no history of clinical or electrographic seizures?		
Recommendation 1	The NCS guideline panel suggests against the use of prophylactic ASM following acute nontraumatic ICH	Weak recommendation, very low quality of evidence	The positive effect of ASM prophylaxis was trivial for prevention of early seizure, late seizure, and mortality. Conversely, there were significantly more adverse events with ASM use, and there was a small but significant increase in worse functional outcomes (mRS scores 4–6) with ASM use
PICO 2	If an ASM is used, should LEV or PHT/fPHT be preferentially used for patients with acute nontraumatic ICH with no history of clinical or electrographic seizures?		
Recommendation 2	If a prophylactic ASM is used after acute nontraumatic ICH, the NCS guideline panel suggests LEV should be used rather than PHT/fPHT for seizure prophylaxis	Weak recommendation, very low quality of evidence	There was a signal toward lower early seizures in one study and fewer adverse events in a meta-analysis of three studies. Additionally, there is widespread use of LEV [34], fewer drug–drug interactions, a more favorable linear pharmacokinetic profile (compared to PHT/fPHT's nonlinear kinetics), and very low albumin binding tendency compared to PHT/fPHT [1, 35]
PICO 3	If an ASM is used, should a long (> 7 days) versus short (≤ 7 days) duration of prophylaxis be used for patients with acute nontraumatic ICH with no history of clinical or electrographic seizures?		
Recommendation 3	If a prophylactic ASM is used after acute nontraumatic ICH, the NCS guideline panel suggests a short duration of use (≤ 7 days) versus a longer duration of use (> 7 days)	Weak recommendation, very low quality of evidence	Strategies using no ASM or short-term ASM (≤ 7 days) were associated with more quality-adjusted life-years than strategies using long-term ASM were in most scenarios [37]. Additionally, the rates of late seizure do not appear to be lower in meta-analyses evaluating 4–6 weeks of ASM versus placebo [1, 20], and there are trends toward higher rates of adverse events among patients who receive ASM versus no ASM [1, 20–23, 33]

Per Grading of Recommendations Assessment, Development, and Evaluation methodology, "strong" recommendations use the term "recommend" and "conditional" recommendations use the term "suggest"

ASM antiseizure medication, *fPHT* fosphenytoin, *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *mRS* modified Rankin scale, *NCS* Neurocritical Care Society, *PHT* phenytoin, *PICO* population, intervention, comparison, and outcome

interventions, bias from missing data, bias in measurement of outcomes, and bias in selection of the reported result.

The certainty of evidence assessment was performed using GRADEPro Guideline Development Tool (GDT) software (McMaster University and Evidence Prime Inc) according to GRADE methodology [18]. In brief, studies that address a specific outcome of interest can be evaluated as a group to determine the certainty of evidence leading to a recommendation. The certainty of evidence may be reduced by the risk of bias, inconsistency (heterogeneity across different studies, typically signified by high I^2 values), indirectness (how closely the studies pertain to the PICO framework), imprecision (unclear effect size due to low event rates, small sample sizes, or wide confidence intervals [CIs]), and publication bias. The certainty of evidence could be increased by a large effect size, a dose–response gradient, or residual confounding that favors the comparator. A final level of confidence rating is generated from this process ranging from very low to high confidence in the estimate of effect (Fig. 1).

Statistical Analyses

All analyses were outcome based and were performed by one study statistician (YY). For each outcome of interest (early seizure, late seizure, adverse events, functional and cognitive outcomes, mortality), we stratified the analysis by ASM type as well as by study design (randomized vs. nonrandomized studies) and tested their differences. The summary statistic used for dichotomous data was relative risk, and the mean difference or standardized mean difference was used, when applicable, for continuous data. Studies that reported adjusted odds ratios were pooled using the method of inverse variance. All meta-analyses were conducted using random-effects models. Substantial heterogeneity was defined as $I^2 \geq 50\%$. All analyses are

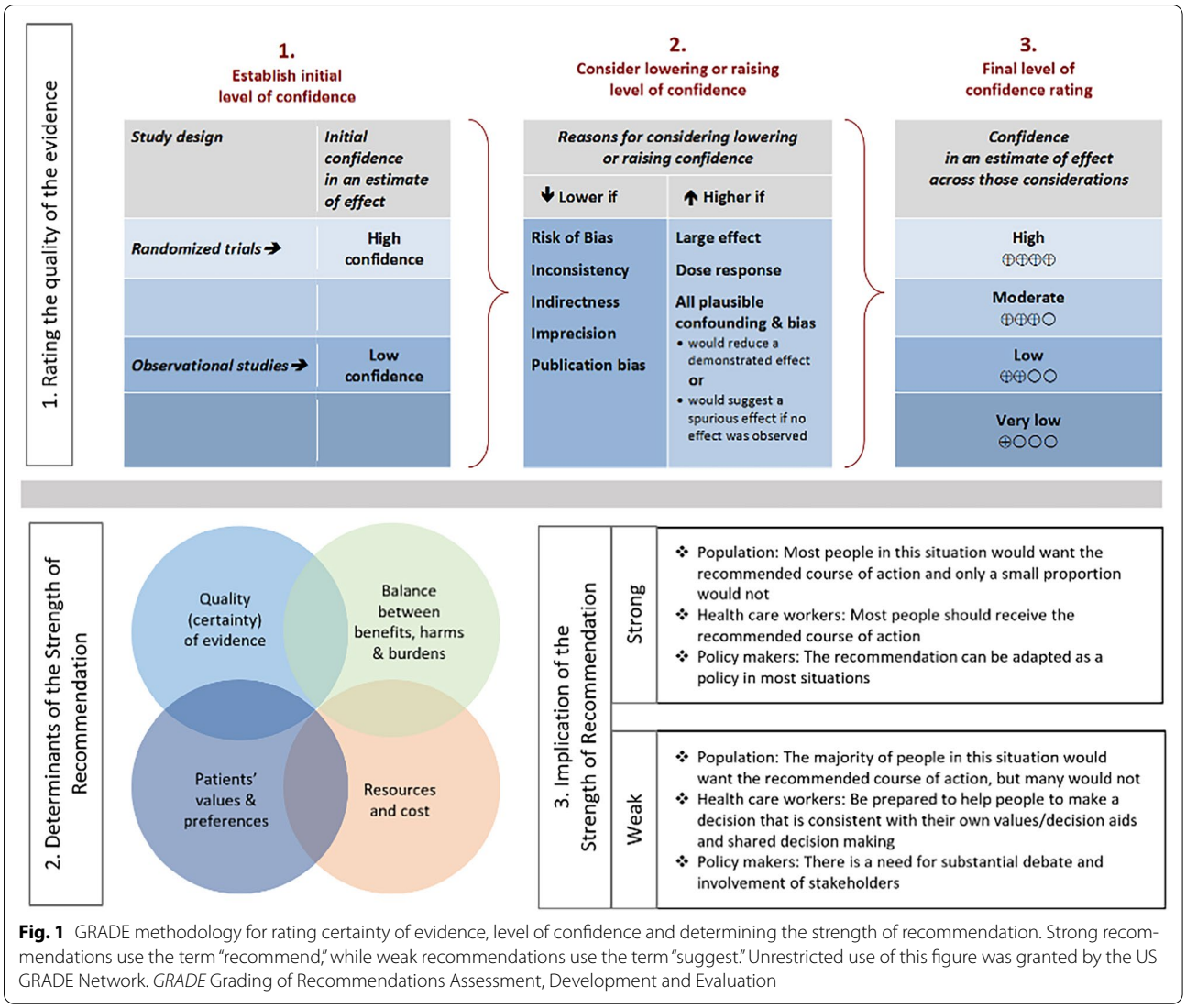

Fig. 1 GRADE methodology for rating certainty of evidence, level of confidence and determining the strength of recommendation. Strong recommendations use the term "recommend," while weak recommendations use the term "suggest." Unrestricted use of this figure was granted by the US GRADE Network. *GRADE* Grading of Recommendations Assessment, Development and Evaluation

presented in forest plots and were performed using Revman 5.4 software (Cochrane, London, UK).

Development of Recommendations

Assessments of judgment for each PICO question were performed using GRADEPro GDT software (McMaster University and Evidence Prime Inc). Final recommendations were based on consideration of the importance of the PICO question, the certainty and confidence level of the evidence, the balance between the desirable and undesirable effects of the intervention, patient values, and the acceptability and feasibility of the recommendation (Fig. 1). Consensus of all panel members was required for final recommendations. Strong recommendations, which imply that the majority of stakeholders would want to adopt the prescribed guidance and policy makers may use the guideline in most situations, are indicated by the phrase "we recommend." Conditional recommendations, which imply that most stakeholders would want to adopt the recommendation, though many might not, and that shared decision-making between patient and practitioner is likely required, are indicated by the verbiage "we suggest." The overall quality (certainty) of evidence was averaged across outcomes for each PICO question and could be categorized as very low, low, moderate, or high. The limitations in the current body of literature and proposals for future avenues of research are discussed with each PICO question.

Recognizing the inherent restrictions of formulated guidelines, the panel has included an "In our practice" section, which highlights current practices that might not be specifically addressed in formal meta-analyses. The pragmatic details of this section were arrived at after an anonymous group survey and panel discussion.

Information presented in this section represents expert consensus. A caveat to this section is that panel members primarily represent academic centers and reflect current practice in the United States. As such, these suggestions may not be generalizable to all settings.

Independent members of the Neurocritical Care Society Guideline Committee reviewed all recommendations. The guideline was available for public comment, and the final version of the document was voted on by the Neurocritical Care Society Board of Directors.

Results

The initial literature search yielded 1,988 articles, of which 15 formed the basis of the recommendations and 13 were included in meta-analyses (Supplementary Fig. 1). Discussion of each PICO question and the relevant literature is detailed below.

ICH PICO 1: Should ASM Versus No ASM be Used in Patients Hospitalized for Acute Nontraumatic ICH with No History of Clinical or Electrographic Seizures?

To Prevent Early Seizure (≤ 14 Days from ICH Onset or During Hospitalization)

A total of eight studies including 3,508 patients were included in a meta-analysis evaluating the outcome of early seizure within 14 days of ICH onset [1, 19–25]. Of these, three evaluated LEV versus no ASM ($n=552$) [1, 19, 22], one evaluated valproic acid (VPA) versus placebo ($n=72$) [20], two evaluated a variety of medications (including LEV, PHT, VPA, and lamotrigine; $n=452$) [21, 23], and two evaluated unspecified ASMs versus no ASM ($n=2{,}432$) [24, 25]. The occurrence of early seizures after ICH appears to be neutral based on two RCTs ($n=122$) [1, 20] and six non-RCTs ($n=3{,}386$) [19, 21–25], with a pooled risk ratio (RR) of 0.97 (95% CI 0.57–1.66, $p=0.91$) (Fig. 2a, b). There was significant heterogeneity across studies ($I^2=72\%$, $P<0.001$) as well as between RCTs and non-RCTs ($I^2=81\%$, $P=0.02$), but no heterogeneity was detected between different ASM types ($I^2=0\%$, $P=0.53$).

We performed a meta-analysis of two small RCTs that suggested a benefit for ASM prophylaxis after ICH for reduction of early seizure (RR 0.31, 95% CI 0.11–0.85, $P=0.02$), with no heterogeneity detected between the studies ($I^2=0\%$) [1, 20]. This study reported a modified intention to treat population after several patients were excluded because of methodological violations. We included the original intention to treat population in our meta-analysis, in which there was no significant difference in seizure events between groups (3 of 24 [12.5%] in the LEV group had early seizure versus 10 of 26 [38%] in the placebo group; RR 0.33, 95% CI 0.10–1.04).

Pooled analysis of two retrospective studies [19, 26] ($n=623$ total patients) that reported adjusted odds ratios for the rates of early seizures (adjusting for age [26], admission National Institutes of Health Stroke Scale [NIHSS] [19] or Glasgow Coma Scale [GCS] [26] score, and cortical ICH location [19, 26]) found that the use of an ASM significantly reduced the risk of early seizure (RR 0.28, 95% CI 0.12–0.62, $P=0.002$; $I^2=0\%$, $P=0.97$ for heterogeneity).

To Prevent Late Seizure (> 14 days from ICH Onset or Post Hospitalization)

Two RCTs ($n=104$) found no difference in late seizures at 12 months post ICH (RR 1.40, 95% CI 0.48–4.13, $P=0.54$, $I^2=0\%$; Fig. 3) [1, 20]. In one study, 36% of patients were lost to follow-up [1], and neither trial evaluated EEG after hospital discharge. Hence, only late clinical seizures were reported.

Adverse Event Rates in ASM Versus No ASM Groups

Adverse events were reported in two RCTs ($n=120$) [1, 20] and three non-RCTs ($n=580$) [21–23], including in patients who received VPA ($n=72$), LEV ($n=190$), or a variety of ASMs (PHT, lamotrigine, LEV, VPA; $n=438$). Some studies reported any adverse events, whereas others stratified events as mild or serious. Only one study used common terminology for adverse events [1]. The duration of observation for adverse events ranged from 72 h [21] to 14 days [22, 23] to 3 months [1] and 1 year [20]. When specified, the number of serious adverse events was used for meta-analyses. Overall, those who received an ASM had significantly higher risk of any adverse event (RR 1.95, 95% CI 1.03–3.68, $P=0.04$; $I^2=35\%$, $P=0.19$ for heterogeneity; Fig. 4a, b). Similarly, there was no heterogeneity across study designs (RCT versus non-RCT) or across ASM types. Of note, two studies detected no differences in behavioral side effects or delirium between patients who received LEV versus no ASM [1, 22].

Functional Outcomes in ASM Versus no ASM Groups

One RCT [1] and five nonrandomized studies [19, 21, 24, 25, 27] included a total of 3,452 patients evaluated poor functional outcome at 90 days post ICH, defined as mRS scores of 4–6. Three studies evaluated LEV versus no ASM [1, 19, 27], and three studies assessed a variety of different ASMs versus no ASM [21, 24, 25]. Meta-analysis favored not using ASM (RR 1.17, 95% CI 1.02–1.35, $P=0.03$; Fig. 5a). There was significant heterogeneity across trials ($I^2=65\%$, $P=0.01$ for heterogeneity). Notably, the point estimate for the single randomized trial that was included favored use of ASM, whereas the point

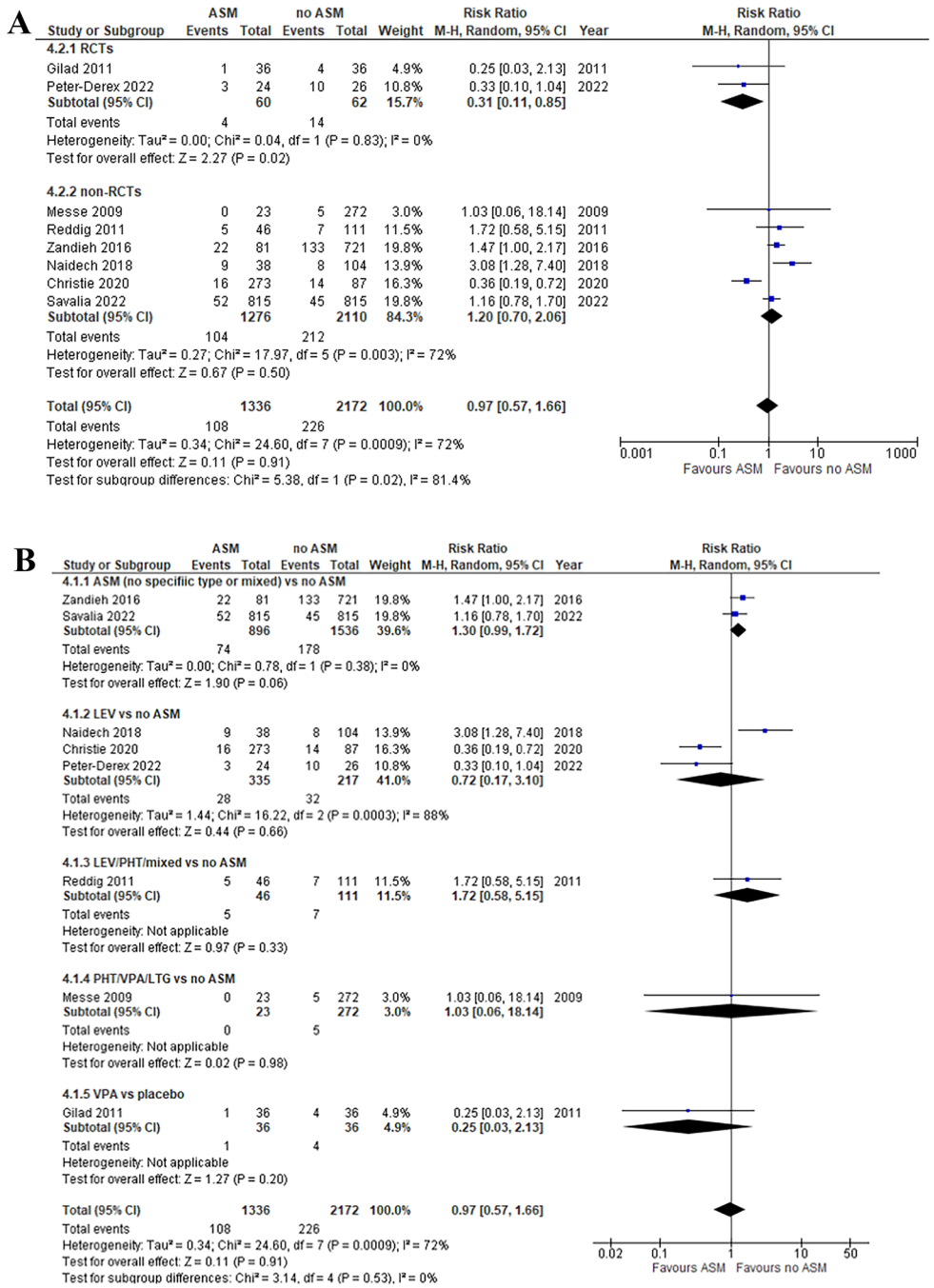

Fig. 2 ICH PICO 1 ASM vs. no ASM for early seizure outcome. Meta-analysis of early seizure outcome among patients with ICH comparing ASM versus no ASM stratified by randomized versus nonrandomized study design (**a**) and ASM type using a random-effects model (**b**). *ASM* anti-seizure medication, *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *LTG* lamotrigine, *M-H* Mantel-Haenszel, *PHT* phenytoin, *RCT* randomized-controlled trial, *VPA* valproic acid

estimate for the observational studies was significantly in favor of no ASM, indicating substantial inconsistency across study types in addition to imprecision in the estimated effect.

Several studies [19, 21, 24, 27–29] also reported adjusted odds ratios for 90-day mRS scores of 4–6 for patients who did or did not receive an ASM after controlling for admission clinical severity (NIHSS [19] or GCS

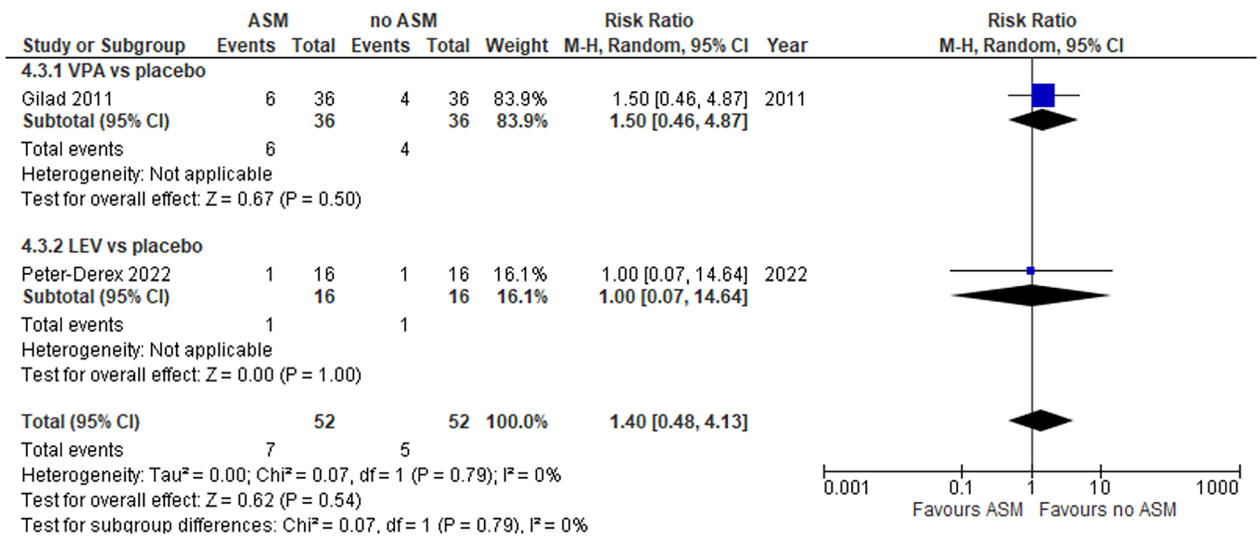

Fig. 3 ICH PICO 1 ASM vs. no ASM for late seizure outcome. Study of late seizure outcome among patients with ICH comparing ASM versus no ASM. *ASM* anti-seizure medication, *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *M-H* Mantel-Haenszel, *RCT* randomized-controlled trial, *VPA* valproic acid

[21, 24, 27] scores), cortical involvement [19, 27], age [21, 24, 27, 28], sex [27], race and ethnicity [27], ICH volume [21, 24, 27, 28], infratentorial ICH location [24], hospital length of stay [28], presence of IVH [21, 24, 27], craniotomy [27], and prior warfarin use [21]. In pooled analysis, there was no significant effect of ASM on 90-day adjusted mRS scores (RR 1.34, 95% CI 0.79–2.27, $P=0.28$; $I^2=79\%$, $P<0.001$ for heterogeneity; Fig. 5b).

Mortality in ASM Versus No ASM Groups

Six studies ($n=3{,}469$), including two RCTs ($n=120$) [1, 20] and four non-RCT studies, [23–25, 28] of mixed ASMs versus placebo ($n=3{,}349$) evaluated mortality. Three studies evaluated mortality at 90 days [24, 25, 28], two studies evaluated mortality at 12 months [1, 28], and one study [23] assessed mortality during hospitalization. Overall, there was no difference in mortality between those who received an ASM and those who did not (RR 0.92, 95% CI 0.73–1.14, $P=0.43$; $I^2=53\%$, $P=0.06$ for heterogeneity; Fig. 6a, b).

Two retrospective studies [24, 28] performed adjusted analysis predicting mortality in patients who received prophylactic PHT [24, 28], VPA [24, 28], LEV [28], or carbamazepine [28] after controlling for age [24, 28], ICH volume [24, 28], the presence of IVH [24], admission GCS [24] score, infratentorial ICH location [24], and hospital length of stay [28]. In pooled analysis, there was no difference in the adjusted risk of death among those who received an ASM versus those who did not (RR 0.86, 95% CI 0.43–1.69, $P=0.66$; $I^2=79\%$, $P=0.03$ for heterogeneity).

Cognitive Outcomes in ASM Versus No ASM Groups

One retrospective study of 142 patients with ICH ($n=38$ received LEV prophylaxis 500 twice daily for a median of 7 days; $n=104$ that did not receive ASM) found that LEV use was associated with worse NeuroQOL (quality of life) cognitive function scores at 1 month after adjusting for age and admission NIHSS score (5.1 points lower, $P=0.01$) [22]. However, at 3 and 12 months, cognitive scores did not differ between patients who had received LEV compared to those who had not.

Limitations in the Literature

There are several limitations that should be mentioned. First, despite data suggesting 22–76% of seizures documented post ICH are subclinical or electrographic-only seizures [2, 3, 30], most studies reported only clinical seizure outcomes, and/or EEG was only performed as needed after a seizure had already occurred [19, 20, 23, 25, 26]. Only two studies required EEG monitoring [1, 22], and only one [1] reported the duration of monitoring. In one RCT that did protocolized continuous EEG monitoring, all seizures detected in the first 72 h post ICH were purely electrographic without a clinical correlate [1]. Hence, seizure outcomes may be underreported in both ASM and no ASM groups.

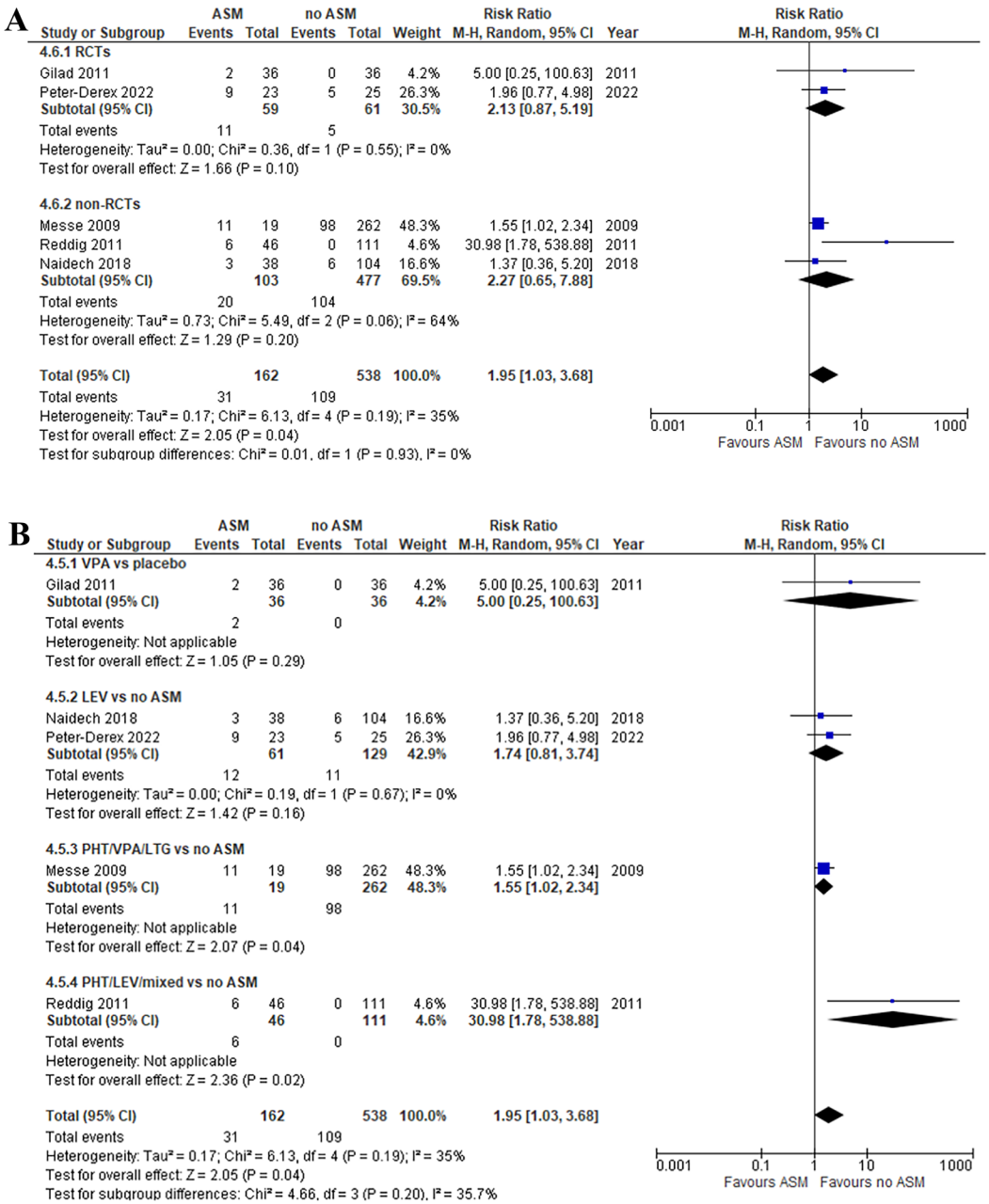

Fig. 4 ICH PICO 1 ASM vs. no ASM for adverse events. Meta-analysis of adverse events among patients with ICH comparing ASM versus no ASM stratified by randomized versus nonrandomized study design (**a**) and ASM type using a random-effects model (**b**). *ASM* anti-seizure medication, *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *LTG* lamotrigine, *M-H* Mantel-Haenszel, *PHT* phenytoin, *RCT* randomized-controlled trial, *VPA* valproic acid

Second, some studies included a variety of different ASMs [21, 23, 24, 26–28], and several studies did not report ASM dosing [19, 21, 23, 24, 26–28], whether drugs were titrated to therapeutic levels [1, 19, 21, 23, 24, 26–29], or the duration of time spent in a therapeutic range [1, 19, 21, 23, 24, 26–29]. Hence, it is unclear if patients in "treatment" groups were actually receiving therapeutic doses of medication. Because ASM levels may have been subtherapeutic in a substantial proportion of

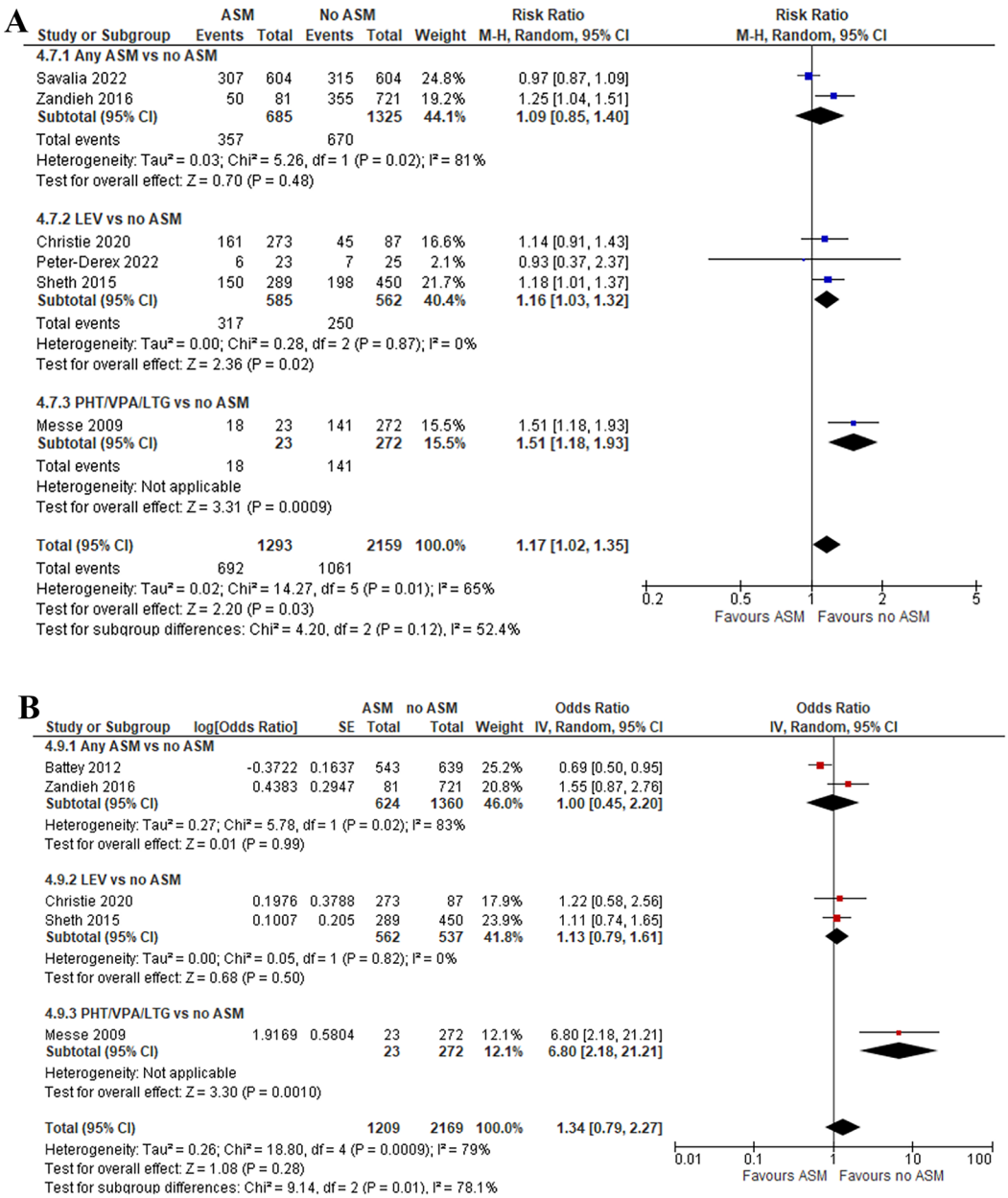

Fig. 5 ICH PICO 1 ASM vs. no ASM for 90-day modified Rankin scale scores of 4–6. Meta-analysis of modified Rankin scale scores 4–6 at 90 days among patients with ICH comparing ASM versus no ASM stratified by ASM type using a random-effects model (**a**) and pooled meta-analysis of adjusted odds ratios for ASM versus no ASM and modified Rankin scale scores 4–6 at 90 days (**b**). *ASM* anti-seizure medication, *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *LTG* lamotrigine, *M-H* Mantel-Haenszel, *PHT* phenytoin, *RCT* randomized-controlled trial, *VPA* valproic acid

patients, the effect size for both benefit and harm may be underestimated.

Third, retrospective studies are subject to treatment biases such that sicker patients may have been more likely to receive prophylactic ASM, or, conversely, the sickest patients may have had limitations in medical treatment due to withdrawal of life-sustaining therapies. None of the studies that reported mortality rates divulged the number of patients who underwent withdrawal of life-sustaining therapy. Because most studies were unblinded, rates of withdrawal may have been unbalanced between ASM and no ASM groups. Although one

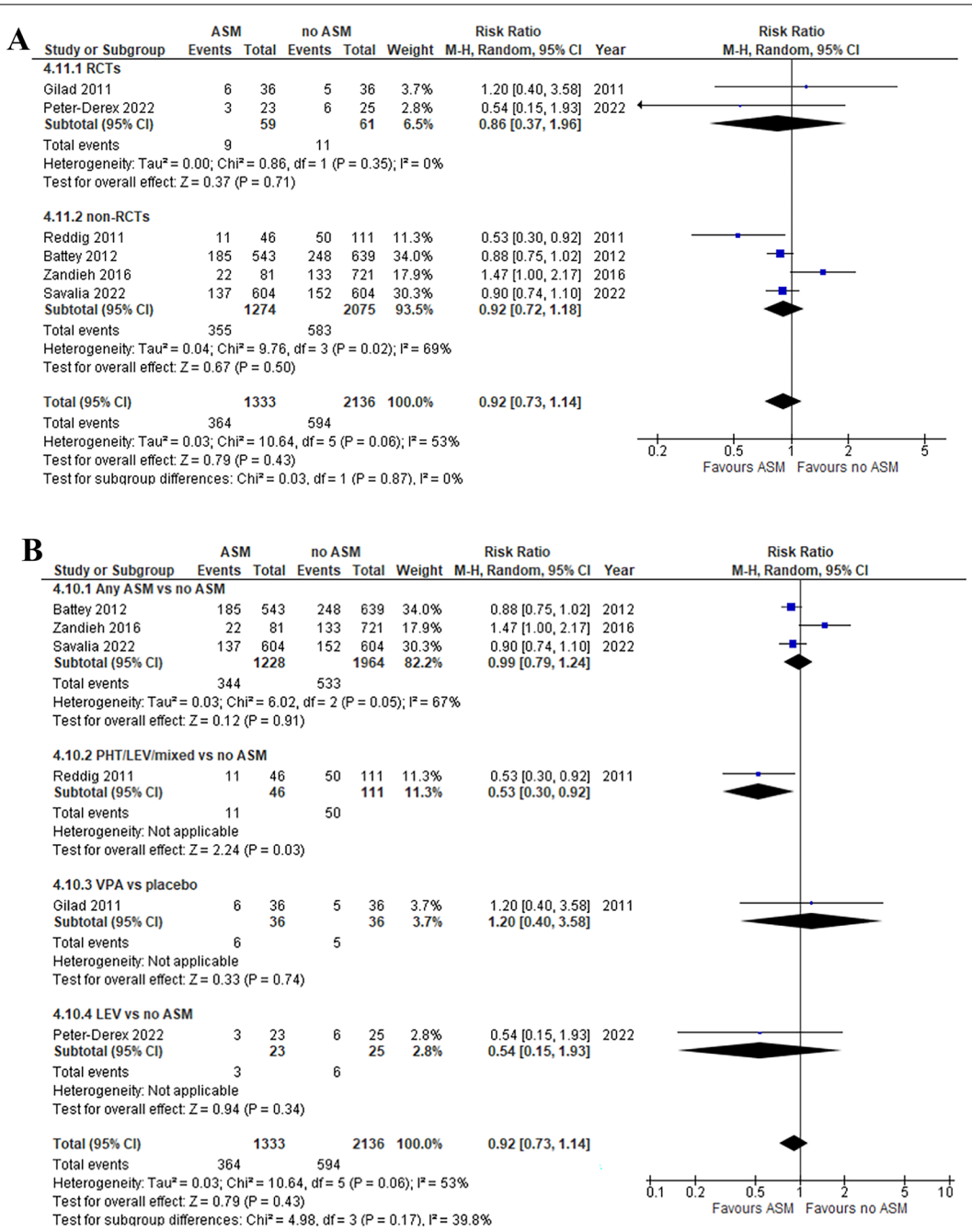

Fig. 6 ICH PICO 1 ASM vs. no ASM for mortality. Meta-analysis of mortality outcome among patients with ICH comparing ASM versus no ASM stratified by randomized versus nonrandomized study design (**a**) and ASM type using a random-effects model (**b**). *ASM* anti-seizure medication, *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *M-H* Mantel-Haenszel, *PHT* phenytoin, *RCT* randomized-controlled trial, *VPA* valproic acid

small randomized trial showed potential benefit for LEV compared to placebo for reducing clinical or electrographic seizure incidence at 72 h, the study was stopped early, resulting in baseline differences between the LEV and placebo groups (worse NIHSS score, younger age, and two-fold higher ICH volumes in the placebo group) [1]. Furthermore, the wide CI for the primary outcome and small study size suggest imprecision in this point estimate, whereas the baseline differences between the LEV and placebo groups inject a substantial risk of type I error. Although several studies reported adjusted odds ratios for either mRS scores of 4–6 at 90 days [19, 21, 24,

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-seizure medication	no anti-seizure medication	Relative (95% CI)	Absolute (95% CI)		
Early seizure												
2	randomised trials	serious	not serious	not serious	very serious[a]	all plausible residual confounding would reduce the demonstrated effect	4/60 (6.7%)	14/62 (22.6%)	RR 0.31 (0.11 to 0.85)	156 fewer per 1,000 (from 201 fewer to 34 fewer)	⊕⊕◯◯ Low	CRITICAL
Early Seizure												
6	observational studies	serious[b]	very serious[c]	serious[d]	serious	all plausible residual confounding would reduce the demonstrated effect	104/1276 (8.2%)	212/2110 (10.0%)	RR 1.20 (0.70 to 2.06)	20 more per 1,000 (from 30 fewer to 107 more)	⊕◯◯◯ Very low	CRITICAL
Late seizure												
2	randomised trials	serious[e]	not serious	not serious	very serious[a]	all plausible residual confounding would reduce the demonstrated effect	7/52 (13.5%)	5/52 (9.6%)	RR 1.40 (0.48 to 4.13)	38 more per 1,000 (from 50 fewer to 301 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events												
2	randomised trials	serious	not serious	serious[f]	serious[a]	all plausible residual confounding would reduce the demonstrated effect	11/59 (18.6%)	5/61 (8.2%)	RR 2.13 (0.87 to 5.19)	93 more per 1,000 (from 11 fewer to 343 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events												
3	observational studies	serious[b]	serious[g]	serious[d]	serious[h]	all plausible residual confounding would reduce the demonstrated effect	20/103 (19.4%)	104/477 (21.8%)	RR 2.27 (0.65 to 7.88)	277 more per 1,000 (from 76 fewer to 1,000 more)	⊕◯◯◯ Very low	CRITICAL
Modified Rankin Scale 4-6 at 90 days												
1	randomised trials	serious	not serious	not serious	very serious	all plausible residual confounding would reduce the demonstrated effect	6/23 (26.1%)	7/25 (28.0%)	RR 0.93 (0.37 to 2.37)	20 fewer per 1,000 (from 176 fewer to 384 more)	⊕⊕◯◯ Low	IMPORTANT
Modified Rankin Scale 4-6 at 90 days												
5	observational studies	very serious[b]	very serious	not serious	serious	all plausible residual confounding would reduce the demonstrated effect	686/1270 (54.0%)	1054/2134 (49.4%)	RR 1.18 (1.02 to 1.36)	89 more per 1,000 (from 10 more to 178 more)	⊕◯◯◯ Very low	IMPORTANT
Mortality												
2	randomised trials	serious	not serious	serious[a]	very serious[a]	all plausible residual confounding would reduce the demonstrated effect	9/59 (15.3%)	11/61 (18.0%)	RR 0.86 (0.37 to 1.96)	25 fewer per 1,000 (from 114 fewer to 173 more)	⊕◯◯◯ Very low	IMPORTANT
Mortality												
4	observational studies	serious[b]	very serious[i]	not serious	serious	all plausible residual confounding would reduce the demonstrated effect	355/1274 (27.9%)	594/2136 (27.8%)	RR 0.92 (0.73 to 1.14)	22 fewer per 1,000 (from 75 fewer to 39 more)	⊕◯◯◯ Very low	IMPORTANT
Cognition (follow-up: 1 months; assessed with: NeuroQoL global cognition)												
1	observational studies	serious	serious	not serious	serious	none	Median NeuroQoL T-score 5.1 points worse with LEV vs to no ASM				⊕◯◯◯ Very low	IMPORTANT

Fig. 7 ICH PICO 1 certainty assessment tables for prophylactic antiseizure medication (ASM) versus no ASM after acute ICH. GRADEPro software generates a certainty level ranging from very low to high based on the risk of bias assessments, inconsistency (heterogeneity across different studies, typically signified by high I^2 values), indirectness (how closely the studies pertain to the PICO), imprecision (unclear effect size due to low event rates, small sample sizes, or wide confidence intervals), and publication bias. The certainty of evidence could be increased by a large effect size, a dose–response gradient, or residual confounding that favors the comparator. *CI* confidence interval, *NeuroQoL* neurological quality of life, *RR* relative risk

27, 28] or mortality [28, 31] in an attempt to account for such confounding, each accounted for different factors in multivariable analyses, making the point estimates of pooled analyses imprecise. Longer-term outcomes (e.g., 6 or 12 months) may be needed to detected differences between groups.

Lastly, there were very limited data regarding adverse events in the ASM group compared to the no ASM group, and only one study [1] used a systematic approach to defining adverse events.

Certainty of Evidence

The certainty of evidence, including risk of bias assessment and effect size, is shown for each outcome of interest (early seizure, late seizure, adverse events, mRS scores 4–6 at 90 days, cognitive outcomes, and mortality), stratified by trial design (randomized versus nonrandomized; Fig. 7). Overall, the certainty of evidence ranged from very low to low. The risk of bias for each article can be found in Supplemental Tables 2 and 3, stratified by article type (RCT versus non-RCT).

Recommendation

In adult patients hospitalized with acute nontraumatic ICH and no history of clinical or electrographic seizure, we suggest against the use of prophylactic ASMs (weak recommendation, very low quality of evidence; Fig. 8).

Justification

The positive effect of ASM prophylaxis was found to be trivial regarding prevention of early seizure, late seizure, and mortality, as the point estimates in all meta-analyses were close to 1.0, and all CIs crossed 1, indicating that if there is a positive effect of ASM prophylaxis, the effect size would appear to be small. Conversely, there were significantly more adverse events with ASM use, and there was a small but significant increase in worse functional outcomes (mRS scores 4–6) with ASM use, although this effect was primarily driven by highly confounded nonrandomized studies. In pooled analysis of adjusted risk of poor functional outcome, the effect of ASM was no longer significant. On balance, taking into consideration that other current guidelines recommend against prophylactic ASM use with ICH [9], the panel

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Fig. 8 ICH PICO 1 summary of judgments for prophylactic ASM (intervention) versus no ASM (comparison) after acute ICH. Generated with GRADEPro GDT software (McMaster University and Evidence Prime Inc). Bold indicates judgment category selected. *ASM* anti-seizure medication, *ICH* intracerebral hemorrhage

suggests against ASM use, while noting the existing literature is of very low certainty because of the aforementioned limitations. It is possible that newer generation ASMs (e.g., lacosamide, brivaracetam) may have better benefit to risk profiles, but larger studies including electrographic seizure outcomes would need to be conducted.

ICH PICO 2: If an ASM is Used, Should LEV or PHT/fPHT be Preferentially Used for Patients with Acute Nontraumatic ICH with No History of Clinical or Electrographic Seizures?

To Prevent Early Seizure (≤ 14 Days from ICH Onset or During Hospitalization)

Only one non-RCT ($n=85$) comparing use of either prophylactic LEV or PHT in patients with ICH evaluated the onset of early seizures [32]. The number of events was small, and there was no significant difference between the two ASMs, although the point estimate favored LEV (RR 0.09, 95% CI 0.00–1.71; Fig. 9).

To Prevent Late Seizure > 14 Days from ICH Onset or Post Hospitalization

There were no eligible studies comparing late seizures between patients treated with LEV and those treated with PHT.

Adverse Events Rates with LEV vs. PHT/fPHT

Three non-RCTs ($n=121$) comparing LEV and PHT use reported adverse events [23, 26, 33]. Although the point estimate appeared to favor LEV, there was no significant difference in adverse events between the groups (pooled RR 2.62, 95% CI 0.74–9.26, $P=0.14$; $I^2=0\%$; Fig. 10). Adverse events reported for PHT included fever [23, 26, 33], rash [33], Stevens–Johnson syndrome [23], renal failure [23], elevated liver function test results [23], and hypotension [23]. Adverse events reported with LEV use included thrombocytopenia [22, 23, 26].

Functional Outcomes with LEV vs. PHT/fPHT

One observational study compared patients who received PHT post ICH (primarily prophylactically,

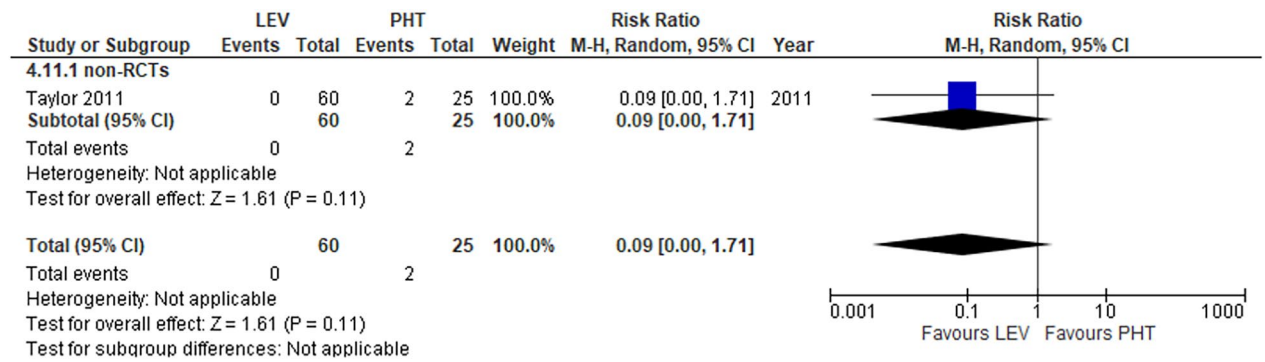

Fig. 9 ICH PICO 2 levetiracetam versus phenytoin/fosphenytoin for early seizure outcome. Meta-analysis of early seizure outcome among patients with ICH comparing levetiracetam to phenytoin/fosphenytoin using a random-effects model. *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *M-H* Mantel-Haenszel, *PHT* phenytoin, *RCT* randomized-controlled trial

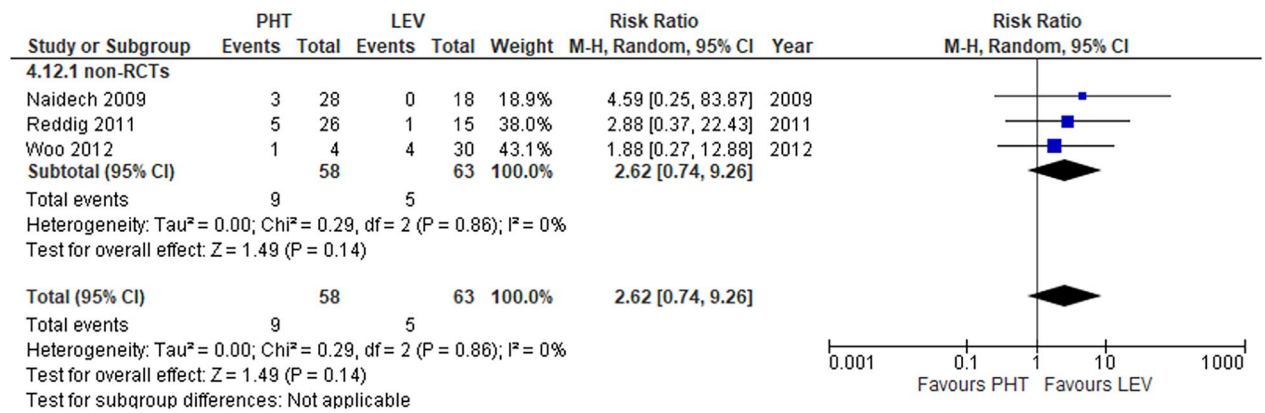

Fig. 10 ICH PICO 2 levetiracetam versus phenytoin/fosphenytoin for adverse events. Meta-analysis of adverse events outcome among patients with ICH comparing levetiracetam to phenytoin/fosphenytoin using a random-effects model. *ICH* intracerebral hemorrhage, *LEV* levetiracetam, *M-H* Mantel-Haenszel, *PHT* phenytoin, *RCT* randomized-controlled trial

although some patients with underlying epilepsy were included) to patients who received LEV prophylaxis or no ASM [33]. After adjusting for age, admission NIHSS score, ICH volume, IVH, and infratentorial location, PHT was significantly associated with worse outcomes (mRS scores 4–6) at 90 days (adjusted odds radio 9.0, 95% CI 1.2–68.5, $P=0.03$).

Limitations in the Literature

Only one study used at least 48 h of continuous EEG data to diagnose seizures in all patients with depressed mental status [22]. All other studies relied on clinical detection of seizures; EEG was only used once a clinical seizure had occurred; otherwise, there was no screening performed for electrographic seizures [23, 26, 32]. The definition of early and late seizures was discordant between studies. One study defined early seizures as occurring within 2 weeks from the ICH onset [22], two studies mentioned within 1 week [23, 26], and another [32] did not define a time frame for early seizure. Three studies reported continuous outcome data with variable measures of functional outcome over a wide range of follow-up time frames, and thus the data could not be pooled for analysis [22, 26, 32]. Additionally, the dosing of LEV was inconsistent across studies, ranging from 250 mg twice daily [32] to 500 mg twice daily [22, 33] to 1,000 mg twice daily [32]. The dose of ASM was not mentioned in two studies [23, 26], and no study evaluated LEV levels. Conversely, most studies titrated PHT to therapeutic free PHT levels [22, 32, 33]. Lastly, no study systematically collected adverse event data in both LEV and PHT populations using standardized tools.

Certainty of Evidence

The overall certainty of evidence for LEV versus PHT was very low (Fig. 11, Supplemental Tables 2 and 3).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	levetiracetam	phenytoin/ fosphenytoin	Relative (95% CI)	Absolute (95% CI)		
Early Seizure												
1	observational studies	serious	not serious	not serious	very serious[a]	strong association	0/60 (0.0%)	2/25 (8.0%)	RR 0.09 (0.00 to 1.71)	73 fewer per 1,000 (from -- to 57 more)	⊕◯◯◯ Very low	CRITICAL
Adverse Events												
3	observational studies	serious	not serious	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect	9/58 (15.5%)	5/63 (7.9%)	RR 2.62 (0.74 to 9.26)	129 more per 1,000 (from 21 fewer to 656 more)	⊕◯◯◯ Very low	CRITICAL
Modified Rankin Score 4-6 at 90 days												
1	observational studies	serious	not serious	not serious	very serious	all plausible residual confounding would reduce the demonstrated effect			OR 9.0 (1.2 to 68.5)	9 fewer per 1,000 (from 69 fewer to 1 fewer)	⊕◯◯◯ Very low	IMPORTANT

Fig. 11 ICH PICO 2 certainty assessment tables for levetiracetam versus phenytoin/fosphenytoin after acute nontraumatic ICH. GRADEPro software generates a certainty level ranging from very low to high based on the risk of bias assessments, inconsistency (heterogeneity across different studies, typically signified by high I^2 values), indirectness (how closely the studies pertain to the PICO), imprecision (unclear effect size due to low event rates, small sample sizes, or wide confidence intervals), and publication bias. The certainty of evidence could be increased by a large effect size, a dose–response gradient, or residual confounding that favors the comparator. *CI* confidence interval, *RR* relative risk

Recommendation

If a prophylactic ASM is used after acute nontraumatic ICH, we suggest LEV should be used over PHT/fPHT for seizure prophylaxis (weak recommendation, very low quality of evidence; Fig. 12).

Justification

This is a conditional recommendation favoring the use of LEV in routine practice due to a signal toward lower early seizures in one study and fewer adverse events in a meta-analysis of three studies. Additional factors contributing to this recommendation include the widespread use of LEV compared to PHT [34] and pharmacological considerations, including fewer drug–drug interactions, a more favorable linear pharmacokinetic profile for LEV, (compared to PHT/fPHT's nonlinear kinetics), and very low albumin binding affinity compared to PHT/fPHT [1, 35].

3.3 ICH PICO 3: If an ASM is Used, Should a Long (> 7 days) Versus Short (≤ 7 Days) Duration of Prophylaxis be Used for Patients with Acute Nontraumatic ICH with No History of Clinical or Electrographic Seizures?

To Predict Quality-Adjusted Life-Years

Only one article was identified that evaluated the impact of short-term (≤ 7 days) versus long-term (> 7 days) seizure prophylaxis on quality-adjusted life-years using a decision analysis model incorporating clinical risk factors and EEG data, specifically the 2HELPS2B score [36] (7-point score based on EEG findings and history of seizure, 0 = low risk, 1 = medium risk, and ≥ 2 = high risk of seizure). The decision analyses found that short-term (7 days) ASM prophylaxis was preferred over long-term ASM use in most scenarios and that the risk-guided strategy using the 2HELPS2B EEG score performed as well as or better than other strategies in most settings.

To Prevent Late Seizure (≥ 14 Days from ICH Onset or Post Hospitalization)

Two small RCTs evaluated late seizure risk. The first evaluated treatment with LEV for 6 weeks [1] versus placebo, and another assessed VPA for 1 month [20] versus placebo. Neither found a difference in rates of late seizure at 12 months between ASM and placebo groups. Notably, neither study used EEG monitoring post hospitalization, and there was significant loss to follow-up in one study [1]. Despite limitations, these trials suggest that there is likely little benefit to long-term ASM use for up to 4–6 weeks.

Adverse Event Rates in Short-Duration Versus Long-Duration ASM

Although the benefit related to long-term ASM prophylaxis appears small, the risk of adverse events may be high [1, 20–23, 26, 33]. Overall, our meta-analysis suggested significantly higher rates of treatment-emergent adverse

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Fig. 12 ICH PICO 2 summary of judgments for prophylactic levetiracetam (intervention) vs. phenytoin/fosphenytoin (comparison) after acute ICH. Generated with GRADEPro GDT software (McMaster University and Evidence Prime Inc). Bold indicates judgment category selected. *ICH* intracerebral hemorrhage

events among those who received ASM versus those who did not (pooled RR 1.95, 95% CI 1.03–3.68, $P=0.04$; Fig. 4). Longer duration of therapy would increase exposure time and conceivably increase risk of adverse events.

Functional Outcomes in Short-Duration Versus Long-Duration ASM

One meta-analyses demonstrated worse functional outcomes (mRS scores 4–6 at 90 days) among those who received ASM versus those who did not (pooled RR 1.17, 95% CI 1.02–1.35, $P=0.03$; Fig. 5). One-month cognitive outcomes also appeared worse among patients who received LEV versus those who did not [22].

Limitations in the Literature

Only one study directly addressed the impact of duration of ASM use [37]. However, because this was a decision analysis, data were modeled using parameter estimates from published literature rather than directly collected data. Additionally, we imputed the impact of longer duration of ASM use across trials assessing ASM given for variable time frames versus placebo. We did not identify any studies that addressed the impact of a 7-day ASM course on early seizures (within 14 days of index ICH), and thus the certainty of the body of literature was downgraded for indirectness. Lastly, although it appears that the risks of ASM side effects may outweigh the benefits, these studies were conducted using primarily older generation ASMs with high-risk profiles. Only one study [1] systematically compared adverse events in ASM versus control groups, and this study found no significant differences in rates of serious adverse events between groups.

Certainty of Evidence

The certainty of evidence was very low (Fig. 13).

Recommendation

If a prophylactic ASM is used after acute nontraumatic ICH, we suggest a short duration of use ($\leq$7 days) versus a longer duration of use (weak recommendation, very low quality of evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-seizure medication	No anti-seizure medication	Relative (95% CI)	Absolute (95% CI)		
Quality-adjusted life years												
1	observational studies	serious	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	Short term (7 day) guided by EEG resulted in 0.25-3.45 more quality-adjusted life years for most scenarios compared to long term primary prophylaxis				⊕◯◯◯ Very low	IMPORTANT
Late seizure												
2	randomised trials	serious	not serious	very serious	very serious	none	7/52 (13.5%)	5/52 (9.6%)	RR 1.40 (0.48 to 4.13)	38 more per 1,000 (from 50 fewer to 301 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events												
2	randomised trials	serious	not serious	very serious	serious	all plausible residual confounding would reduce the demonstrated effect	11/59 (18.6%)	5/61 (8.2%)	RR 2.13 (0.87 to 5.19)	93 more per 1,000 (from 11 fewer to 343 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events												
3	observational studies	serious	serious	very serious	serious	all plausible residual confounding would reduce the demonstrated effect	20/103 (19.4%)	104/477 (21.8%)	RR 2.27 (0.65 to 7.88)	277 more per 1,000 (from 76 fewer to 1,000 more)	⊕◯◯◯ Very low	CRITICAL
Modified Rankin Scale 4-6 at 90 days												
1	randomised trials	serious	not serious	very serious	very serious	all plausible residual confounding would reduce the demonstrated effect	6/23 (26.1%)	7/25 (28.0%)	RR 0.93 (0.37 to 2.37)	20 fewer per 1,000 (from 176 fewer to 384 more)	⊕◯◯◯ Very low	IMPORTANT
Modified Rankin Scale 4-6 at 90 days												
5	observational studies	very serious	very serious	very serious	serious	all plausible residual confounding would reduce the demonstrated effect	686/1270 (54.0%)	1054/2134 (49.4%)	RR 1.18 (1.02 to 1.36)	89 more per 1,000 (from 10 more to 178 more)	⊕◯◯◯ Very low	IMPORTANT
Cognitive function												
1	observational studies	serious	serious	very serious	serious	none	Median NeuroQoL T-score 5.1 points worse with LEV compared to no ASM				⊕◯◯◯ Very low	

Fig. 13 ICH PICO 3 certainty assessment tables for long versus short duration of ASM after acute ICH. GRADEPro software generates a certainty level ranging from very low to high based on the risk of bias assessments, inconsistency (heterogeneity across different studies, typically signified by high I^2 values), indirectness (how closely the studies pertain to the PICO), imprecision (unclear effect size due to low event rates, small sample sizes, or wide confidence intervals), and publication bias. The certainty of evidence could be increased by a large effect size, a dose–response gradient, or residual confounding that favors the comparator. *ASM* anti-seizure medication, *CI* confidence interval, *EEG* electroencephalogram, *LEV* levetiracetam, *NeuroQoL* neurological quality of life, *RR* relative risk

Justification

One well-conducted decision analysis study found that strategies using no ASM or short-term ASM (≤7 days) were associated with more quality-adjusted life-years than strategies using long-term ASM were in most scenarios [37]. Additionally, the rates of late seizure (14 days to 12 months post ICH) do not appear to be lower in meta-analyses evaluating 4–6 weeks of ASM versus placebo [1, 20], and there are trends toward higher rates of adverse events among patients who receive ASM versus no ASM [1, 20–23, 33]. Furthermore, 90-day functional (mRS scores 4–6) [1, 19, 21, 24, 27, 28] and cognitive [22] outcomes were worse in ASM versus no ASM groups. Taken together, these data suggest minimizing prophylactic ASM and favor short-term rather than long-term use (Fig. 14).

Discussion

In an effort to add pragmatic clinical guidance and contextualize the evidence-based GRADE recommendations, the committee developed consensus expert opinion statements termed "In our practice" to frame prophylactic ASM use for each PICO question.

PICO 1: Use of ASM vs. No ASM: In Our Practice

Because the risk of electrographic-only (nonconvulsive) seizures post ICH is high [1–3] and the single study that tracked electrographic seizure outcomes found a benefit for ASM use [1], panel members concurred that they typically maintain a high level of vigilance for seizure in patients with ICH. Most panel members reported use of continuous EEG monitoring for both deep and lobar ICH locations, although EEG monitoring was less frequently used in patients with infratentorial ICH, where the risk of seizure is likely small. A variety of scales are available to estimate the risk of seizure and guide use of ASM prophylaxis, including the 2HELPS2B score [36, 38] and the CAVE score [4]. Depending on individual risk/benefit assessment and value placed on seizure avoidance versus ASM side effects, prophylactic ASM may be considered for a medium seizure risk (12% risk, 2HELPS2B score = 1) or high seizure risk (> 25% risk, 2HELPS2B score ≥ 2), whereas ASM prophylaxis may be avoided in those with a low seizure risk (2HELPS2B score = 0, < 5% risk).

In high-risk cases in which continuous video EEG monitoring is indicated but not readily available (e.g., comatose patients with limited examinations, or patients

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

Fig. 14 ICH PICO 3 summary of judgments for recommending for long (intervention) versus short (comparison) duration of ASM use after acute ICH. Generated with GRADEPro GDT software (McMaster University and Evidence Prime Inc). Bold indicates judgment category selected. *ICH* intracerebral hemorrhage

with a prior seizure), shorter duration routine EEG and/or limited montage rapid response EEG [39–41] can be employed, although the sensitivity and specificity of both are lower than that for continuous EEG [42], and interpretation of artifact is challenging when there is no accompanying video. When EEG data are not available, the CAVE score [4], which was developed to predict late seizures (>7 days) after ICH, is based entirely on clinical variables, including cortical involvement, age < 65 years, ICH volume > 10 mL, and the occurrence of early seizures (≤7 days from ICH). The risk of late seizures ranged from 0.6% for a score of 0 to 46% for a score of 4. Nearly 60% of patients with late seizure did not have a prior early seizure, underscoring the importance of posthospitalization neurological follow-up in patients with ICH.

Overall, the committee members concurred that in general, they do not use prophylactic ASM in patients with ICH. However, most would use EEG features, including the presence of epileptiform discharges, to identify a subset of patients who may be at high seizure risk and/or may benefit from prophylactic ASM.

PICO 2: LEV vs. PHT/fPHT: In Our Practice

Although early analyses suggested a cost-effectiveness benefit for the use of PHT over LEV [43], the introduction of generic forms of both oral and intravenous LEV in 2009 and 2011, respectively, eliminated this cost differential, especially when accounting for the expense of PHT-related complications. Given factors such as drug interactions, the requirement for dose titration and laboratory monitoring due to albumin binding, and similar cost to LEV, PHT has become a less palatable ASM choice [44]. When LEV is used, a reasonable starting dose for patients with creatinine clearance > 30 mL/min is 750–1,000 mg twice daily. In a prospective study of adult neurocritically ill patients (including those with traumatic brain injury, subarachnoid hemorrhage, ICH, and supratentorial neurosurgery), compared to low-dose LEV (500 mg twice daily), use of higher doses (750–1,000 mg BID) was associated with a two-fold increased odds of achieving target drug levels and a 68% lower odds of clinical or electrographic seizure [45]. Patients with augmented renal clearance (≥130 mL/min) may require even higher or more frequent doses to reach target serum

levels. Lower doses (e.g., 500 mg once or twice daily) are typically reserved for patients with creatinine clearance ≤ 30 mL/min. When possible, many panel members trend LEV levels and adjust LEV dosing to maintain target serum levels. Although behavioral side effects may dissuade some practitioners from using LEV, alternative ASMs (e.g., brivaracetam) that are available in intravenous formulation (which may be preferred in critically ill patients or those with questionable enteral absorption) may be more expensive than generic LEV. An indirect comparison analysis of 24 RCTs including 8,540 patients found no differences in efficacy when comparing eslicarbazepine, lacosamide, perampanel, or brivaracetam to LEV; however, lacosamide and perampanel appeared to have higher rates of treatment-emergent adverse events and higher withdrawal rates due to adverse events, whereas brivaracetam had similar tolerability compared to LEV [46]. Nonetheless, there are some data to support fewer psychiatric side effects with both lacosamide and brivaracetam compared to LEV and older generation ASMs [47, 48], which may make these drugs preferred in certain circumstances.

PICO 3: Duration of ASM Use: In Our Practice

As mentioned in PICO 1, most of the panel would defer primary prophylaxis at the time of admission and use continuous EEG monitoring to evaluate for high-risk electrographic features. When EEG monitoring suggests moderate-high seizure risk (i.e., 2HELPS2B score ≥ 1 or epileptiform discharges seen), some panel members would initiate primary ASM prophylaxis. In patients without high-risk EEG features or when EEG cannot be performed, panel members who initiate primary ASM prophylaxis would use it only for 7 days, not longer. If an early seizure occurs, panel members universally would initiate ASM treatment. However, the duration of primary prophylaxis or treatment (secondary prophylaxis following an index seizure) varies substantially among panel members when EEG demonstrates high-risk features. Many panel members would opt to continue ASM post discharge and reevaluate the patient in follow-up, taking into account recurrent seizures post discharge and medication-emergent side effects. Several members routinely perform repeat EEG (ambulatory preferred) to assess for ongoing high-risk features prior to weaning ASM at 3–6 months post discharge. Counseling on driving and operation of heavy machinery is routinely provided in accordance with state and local guidelines by panel members who treat patients with epilepsy in the outpatient setting.

In summary, although most of the panel does not use ASM prophylaxis a priori in every patient with ICH, most panel members perform continuous EEG monitoring and consider primary ASM prophylaxis in patients with high-risk EEG features, including the presence of epileptiform discharges. All panel members report that they treat clinical or electrographic seizures with ASM and often continue EEG monitoring for a longer duration with continuous video EEG or repeated intermittent EEG. If an ASM is used for seizure prophylaxis, all panel members noted a preference for LEV over PHT. Many panel members use newer agents, including lacosamide and brivaracetam. If an ASM were used for a patient without clinical seizure or high-risk EEG features, all panel members reported that they would minimize the duration of use to ≤ 7 days.

Conclusions

A summary of recommendations is listed in Table 1. The panel suggests against the use of prophylactic ASM following acute nontraumatic ICH, and if an ASM is initiated, the panel suggests a short duration (≤ 7 days) of LEV, as opposed to PHT/fPHT. Continuous EEG may help risk stratify patients for prophylaxis. The panel recognizes substantial limitations in the existing literature, including ascertainment bias for seizure outcomes due to the limited use of continuous EEG monitoring in most studies and the fact that the majority of seizures post ICH are either subtle or purely electrographic [2, 3]. Additional limitations include possible underdosing of ASM, failure to routinely titrate ASM to target levels, and lack of systematic acquisition of ASM-emergent adverse events. The ideal duration of prophylactic ASM use, particularly in the context of epileptiform discharges or ictal-interictal continuum phenomenon, is unknown. ASMs other than LEV or PHT/fPHT may be preferred in certain settings, although there were inadequate data to evaluate other medications. Furthermore, there may be cost implications related to the decision to use ASM prophylaxis; however, this outcome was beyond the scope of this guideline. Well-designed RCTs evaluating modern ASMs are needed to better quantify the risks and benefits of prophylactic ASM use in patients with acute nontraumatic ICH.

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