Stroke

AHA/ASA GUIDELINE

# 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

*Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.*

*Endorsed by the Society of Vascular and Interventional Neurology*

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

*Endorsed by the Neurocritical Care Society*

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**Key Words:** AHA Scientific Statements ■ cerebral amyloid angiopathy ■ cerebral hemorrhage ■ intracranial hemorrhage ■ prevention ■ recovery ■ treatment

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## TOP 10 TAKE-HOME MESSAGES FOR THE MANAGEMENT OF PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE GUIDELINE

1. The organization of health care systems is increasingly recognized as a key component of optimal stroke care. This guideline recommends development of regional systems that provide initial intracerebral hemorrhage (ICH) care and the capacity, when appropriate, for rapid transfer to facilities with neurocritical care and neurosurgical capabilities.
2. Hematoma expansion is associated with worse ICH outcome. There is now a range of neuroimaging markers that, along with clinical markers such as time since stroke onset and use of antithrombotic agents, help to predict the risk of hematoma expansion. These neuroimaging markers include signs detectable by noncontrast computed tomography, the most widely used neuroimaging modality for ICH.
3. ICHs, like other forms of stroke, occur as the consequence of a defined set of vascular pathologies. This guideline emphasizes the importance of, and approaches to, identifying markers of both microvascular and macrovascular hemorrhage pathogeneses.
4. When implementing acute blood pressure lowering after mild to moderate ICH, treatment regimens that limit blood pressure variability and achieve smooth, sustained blood pressure control appear to reduce hematoma expansion and yield better functional outcome.

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5. ICH while anticoagulated has extremely high mortality and morbidity. This guideline provides updated recommendations for acute reversal of anticoagulation after ICH, highlighting use of protein complex concentrate for reversal of vitamin K antagonists such as warfarin, idarucizumab for reversal of the thrombin inhibitor dabigatran, and andexanet alfa for reversal of factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban.
6. Several in-hospital therapies that have historically been used to treat patients with ICH appear to confer either no benefit or harm. For emergency or critical care treatment of ICH, prophylactic corticosteroids or continuous hyperosmolar therapy appears to have no benefit for outcome, whereas the use of platelet transfusions outside the setting of emergency surgery or severe thrombocytopenia appears to worsen outcome. Similar considerations apply to some prophylactic treatments historically used to prevent medical complications after ICH. Use of graduated knee- or thigh-high compression stockings alone is not an effective prophylactic therapy for prevention of deep vein thrombosis, and prophylactic antiseizure medications in the absence of evidence for seizures do not improve long-term seizure control or functional outcome.
7. Minimally invasive approaches for evacuation of supratentorial ICHs and intraventricular hemorrhages, compared with medical management alone, have demonstrated reductions in mortality. The clinical trial evidence for improvement of functional outcome with these procedures is neutral, however. For patients with cerebellar hemorrhage, indications for immediate surgical evacuation with or without an external ventricular drain to reduce mortality now include larger volume (>15 mL) in addition to previously recommended indications of neurological deterioration, brainstem compression, and hydrocephalus.
8. The decision of when and how to limit life-sustaining treatments after ICH remains complex and highly dependent on individual preference. This guideline emphasizes that the decision to assign do not attempt resuscitation status is entirely distinct from the decision to limit other medical and surgical interventions and should not be used to do so. On the other hand, the decision to implement an intervention should be shared between the physician and patient or surrogate and should reflect the patient's wishes as best as can be discerned. Baseline severity scales can be useful to provide an overall measure of hemorrhage severity but should not be used as the sole basis for limiting life-sustaining treatments.
9. Rehabilitation and recovery are important determinants of ICH outcome and quality of life. This guideline recommends use of coordinated multidisciplinary inpatient team care with early assessment of discharge planning and a goal of early supported discharge for mild to moderate ICH. Implementation of rehabilitation activities such as stretching and functional task training may be considered 24 to 48 hours after moderate ICH; however, early aggressive mobilization within the first 24 hours after ICH appears to worsen 14-day mortality. Multiple randomized trials did not confirm an earlier suggestion that fluoxetine might improve functional recovery after ICH. Fluoxetine reduced depression in these trials but also increased the incidence of fractures.
10. A key and sometimes overlooked member of the ICH care team is the patient's home caregiver. This guideline recommends psychosocial education, practical support, and training for the caregiver to improve the patient's balance, activity level, and overall quality of life.

## PREAMBLE

Since 1990, the American Heart Association (AHA)/American Stroke Association (ASA) has translated scientific evidence into clinical practice guidelines with recommendations to improve cerebrovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cerebrovascular care. The AHA/ASA sponsors the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts.

Clinical practice guidelines for stroke provide recommendations applicable to patients with or at risk of developing cerebrovascular disease. The focus is on medical practice in the United States, but many aspects are relevant to patients throughout the world. Although it must be acknowledged that guidelines may be used to inform regulatory or payer decisions, the core intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment; furthermore, the recommendations set forth should be considered in the context of individual patient values, preferences, and associated conditions.

The AHA/ASA strives to ensure that guideline writing groups contain requisite expertise and are representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different sexes, races, ethnicities, intellectual perspectives, geographic regions, and scopes of clinical practice and by inviting organizations and professional societies with related interests and expertise to participate as endorsers. The AHA/ASA has rigorous policies and methods for development of guidelines that limit bias and prevent improper influence. The complete policy on relationships with industry and

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other entities (RWI) can be found at https://professional.heart.org/-/media/phd-files/guidelines-and-statements/policies-devolopment/aha-asa-disclosure-rwi-policy-5118.pdf?la=en.

Beginning in 2017, numerous modifications to AHA/ASA guidelines have been implemented to make guidelines shorter and enhance user-friendliness. Guidelines are written and presented in a modular knowledge chunk format; each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text, and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided to facilitate quick access and review. Other modifications to the guidelines include the addition of Knowledge Gaps and Future Research segments in some sections and a web guideline supplement (Online Data Supplement) for useful but noncritical tables and figures.

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*Chair, AHA Stroke Council Scientific Statement Oversight Committee*

## 1. INTRODUCTION

Approximately 10% of the 795 000 strokes per year in the United States are intracerebral hemorrhages (ICHs),[1] defined by brain injury attributable to acute blood extravasation into the brain parenchyma from a ruptured cerebral blood vessel. The clinical impact of ICH appears disproportionately high among lower-resource populations both in the United States and internationally. In US-based studies, ICH incidence has been reported to be ≈1.6-fold greater among Black than White people[2] and 1.6-fold greater among Mexican American than non-Hispanic White people.[3] Internationally, ICH incidence is substantially higher in low- and middle-income versus high-income countries, both as a proportion of all strokes and in absolute incidence rates.[4,5]

Several additional features of ICH make it a greater public health threat than conveyed by incidence numbers alone. ICH is arguably the deadliest form of acute stroke, with early-term mortality about 30% to 40% and no or minimal trend toward improvement over more recent time epochs.[6–9] Incidence of ICH increases sharply with age and is therefore expected to remain substantial as the population ages, even with counterbalancing public health improvements in blood pressure (BP) control.[8] Another growing source of ICH is more widespread use of anticoagulants,[10] a trend likely to counterbalance the reduced ICH risk associated with increasing prescription of direct oral anticoagulants (DOACs) relative to vitamin K antagonists (VKAs).[11]

ICH thus remains in need of novel treatments and improved application of established approaches for every aspect of the disease: primary and secondary prevention, acute inpatient care, and poststroke rehabilitation and recovery. This guideline seeks to synthesize data in the ICH field into practical recommendations for clinical practice.

### 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based and supported by extensive evidence review. A search for literature derived from research principally involving human subjects, published in English, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases relevant to this guideline was conducted between October 2020 and March 2021. Additional trials published between March 2021 and November 2021 that affected the content, Class of Recommendation (COR), or Level of Evidence (LOE) of a recommendation were included when appropriate. For specific search terms used, readers are referred to the Online Data Supplement, which contains the final evidence tables summarizing the evidence used by the guideline writing group to formulate recommendations. In addition, the guideline writing group reviewed documents related to subject matter previously published by the AHA/ASA. References selected and published in the present document are representative and not all inclusive.

Each topic area was assigned a primary writer and a primary and sometimes secondary reviewer. Author assignments were based on the areas of expertise of the members of the guideline writing group and their lack of any RWI related to the section material. All recommendations were fully reviewed and discussed among the full guideline writing group to allow diverse perspectives and considerations for this guideline. Recommendations were then voted on, and a modified Delphi process was used to reach consensus. Guideline writing group members who had RWI that were relevant to certain recommendations were recused from voting on those particular recommendations. All recommendations in this guideline were agreed to by between 88.9% and 100% of the voting guideline writing group members.

### 1.2. Organization of the Writing Group

The guideline writing group consisted of vascular neurologists, neurocritical care specialists, neurological surgeons, an emergency physician, a hematologist, a rehabilitation medicine physician, a board-certified acute care nurse practitioner, a fellow-in-training, and a lay/patient representative. The writing group included representatives from the AHA/ASA, the American Association of Neurological Surgeons/Congress of Neurological Surgeons, and the American Academy of Neurology. Appendix 1 of this document lists guideline writing group members' relevant RWI and other entities. For the purposes of full transparency, the guideline writing group members' comprehensive disclosure information is available online.

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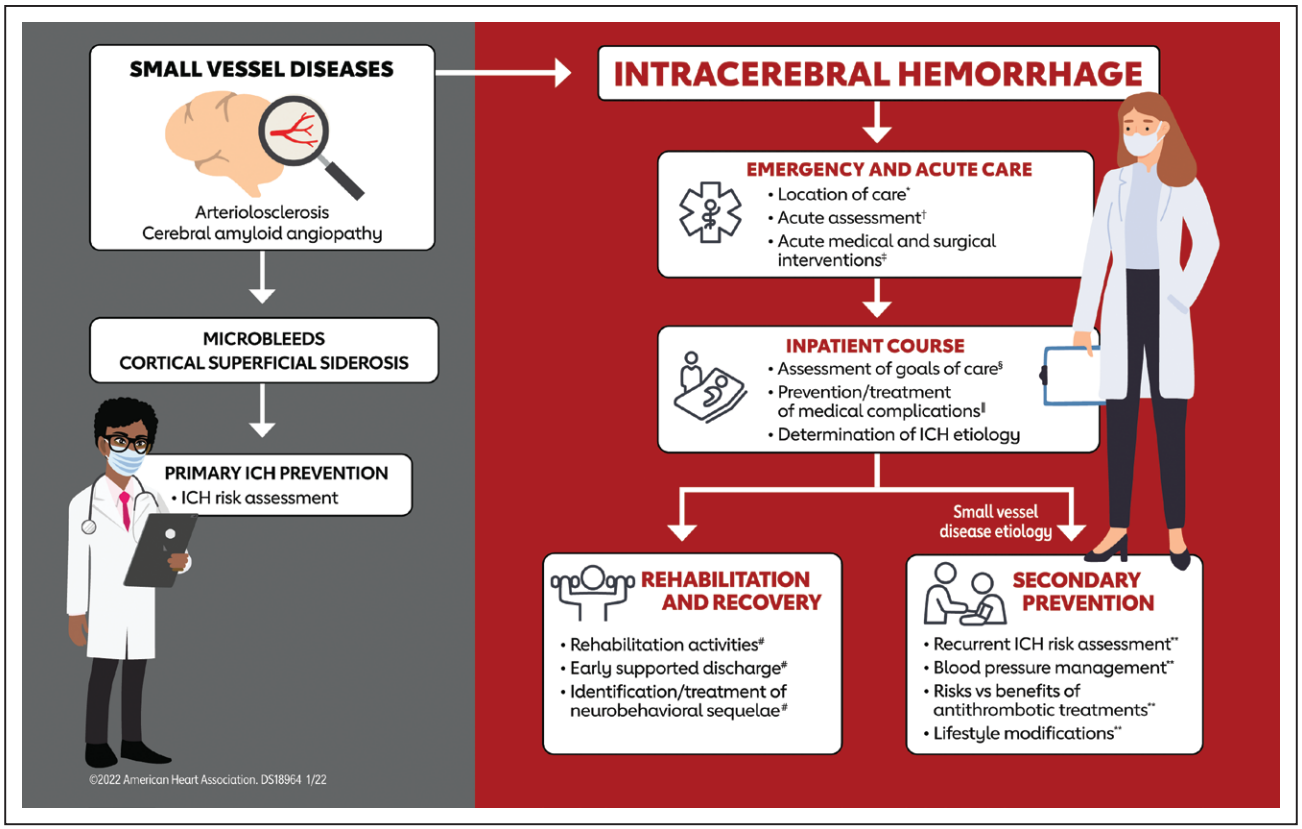


**Figure 1. Guideline overview for primary ICH.**
ICH indicates intracerebral hemorrhage. Recommendations on the topics above can be found in the guideline in the sections indicated: *Sections 3 and 5. †Section 4. ‡Sections 5 and 6. §Section 7. ‖Section 5. #Section 8. **Section 9.

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## 1.3. Document Review and Approval

This document was reviewed by the AHA Stroke Council Scientific Statement Oversight Committee, the AHA Science Advisory and Coordinating Committee, and the AHA Executive Committee; reviewers from the American Academy of Neurology, the Society of Vascular and Interventional Neurology, and the American Association of Neurological Surgeons/Congress of Neurological Surgeons; and 53 individual content reviewers. Appendix 2 lists reviewers' comprehensive disclosure information.

## 1.4. Scope of the Guideline

This guideline addresses the diagnosis, treatment, and prevention of ICH in adults and is intended to update and replace the AHA/ASA 2015 ICH guideline.[12] This 2022 guideline is limited explicitly to spontaneous ICHs that are not caused by head trauma and do not have a visualized structural cause such as vascular malformation, saccular aneurysm, or hemorrhage-prone neoplasm. These hemorrhages without a demonstrated structural or traumatic cause are often referred to as primary ICH (see further comment on this terminology in Section 2.1, Small Vessel Disease Types). This guideline thus does not overlap with AHA/ASA guidelines or scientific statements on the treatment of arteriovenous malformations,[13] aneurysmal subarachnoid hemorrhage,[14] or unruptured saccular aneurysms.[13,15] This guideline does, however, address imaging approaches to ICH that help differentiate primary ICH from these secondary causes.

This guideline aims to cover the full course of primary ICH (Figure 1), from the location and organization of emergency care (Section 3), initial diagnosis and assessment (Section 4), and acute medical and surgical interventions (Sections 5.1, 5.2, and 6) to further inpatient care of post-ICH complications (Sections 5.3–5.5), goals of care assessment (Section 7), rehabilitation and recovery (Section 8), and secondary prevention of recurrent ICH (Section 9). Because of the substantial differences in pathogenesis and course between ICH and ischemic stroke, the writing group sought, when possible, to base its recommendations on data derived specifically from ICH patient groups. Some aspects of inpatient medical care and post-ICH rehabilitation are likely to be similar between patients with ICH and patients with ischemic stroke, however. Readers are therefore referred to relevant AHA/ASA guidelines and scientific statements for ischemic stroke in these overlapping areas.[16,17] Table 1 is a list of associated AHA/ASA guidelines and scientific statements that may be of interest to the reader.

Another area where this ICH guideline interfaces with prior ischemic stroke guidelines is the challenging area of antithrombotic agent use in patients after ICH who are at risk for both recurrent ICH and ischemic stroke

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**Table 1. Associated AHA/ASA Guidelines and Statements**

| Title | Organization | Publication year |
|---|---|---|
| AHA/ASA guidelines | | |
| 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association | AHA/ASA | 2021 |
| 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines | ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA | 2017 |
| Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2016 |
| Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2015 |
| Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2015 |
| Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2014 |
| Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2012 |
| AHA/ASA scientific statements | | |
| Care of the Patient With Acute Ischemic Stroke (Prehospital and Acute Phase of Care): Update to the 2009 Comprehensive Nursing Care Scientific Statement: A Scientific Statement From the American Heart Association | AHA/ASA | 2021 |
| Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2017 |
| Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2017 |
| Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association | AHA/ASA | 2014 |

AAPA indicates American Association of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASA, American Stroke Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; NMA, National Medical Association; and PCNA, Preventive Cardiovascular Nurses Association.

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(Section 9.1.3, Management of Antithrombotic Agents). This guideline does not attempt to reassess the extensive literature on assessment of future ischemic stroke risk and instead refers the reader to existing AHA guidelines on primary and secondary ischemic stroke prevention.[18,19]

This ICH guideline has a new section on assessment of ICH risk in individuals with no prior ICH but with neuroimaging findings such as cerebral microbleeds or cortical superficial siderosis suggestive of a hemorrhage-prone microvasculopathy. This topic, which was also previously discussed in an AHA scientific statement on the wider area of silent cerebrovascular disease,[20] does not fall strictly under the heading of ICH management. This guideline writing group nonetheless included the section (9.2, Primary ICH Prevention in Individuals With High-Risk Imaging Findings) because of its close relationship to the considerations used for secondary prevention of recurrent ICH (Section 9.1, Secondary Prevention) and the high frequency with which these small hemorrhagic lesions are detected as incidental findings on magnetic resonance imaging (MRI) performed for other indications. Evidence on how to interpret and act on incidental hemorrhagic lesions remains limited but is likely to grow with the widespread incorporation of blood-sensitive MRI methods into research studies and clinical practice.

## 1.5. COR and LOE

Recommendations are designated with both a COR and an LOE. The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 2).

## Abbreviations

| Abbreviation | Meaning/Phrase |
|---|---|
| ADL | activities of daily living |
| AF | atrial fibrillation |
| AHA | American Heart Association |
| aPCC | activated prothrombin complex concentrate |
| ASA | American Stroke Association |
| ATACH-2 | Antihypertensive Treatment of Acute Cerebral Hemorrhage II |
| AVERT | A Very Early Rehabilitation Trial |
| BP | blood pressure |
| CAA | cerebral amyloid angiopathy |
| CLEAR III | Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III |

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| Abbreviation | Meaning/Phrase |
|---|---|
| CLOTS | Clots in Legs or Stockings After Stroke |
| COR | Class of Recommendation |
| CPP | cerebral perfusion pressure |
| CT | computed tomography |
| CTA | computed tomography angiography |
| DBP | diastolic blood pressure |
| DIAGRAM | Diagnostic Angiography to Find Vascular Malformations |
| DNAR | do not attempt resuscitation |
| DOAC | direct oral anticoagulant |
| DSA | digital subtraction angiography |
| DVT | deep vein thrombosis |
| ED | emergency department |
| EIBPL | early intensive blood pressure lowering |
| EMS | emergency medical services |
| ERICH | Ethnic/Racial Variations of Intracerebral Hemorrhage |
| EVD | external ventricular drain/drainage |
| FFP | fresh-frozen plasma |
| 4-F PCC | 4-factor prothrombin complex concentrate |
| GCS | Glasgow Coma Scale |
| HE | hematoma expansion |
| HR | hazard ratio |
| ICH | intracerebral hemorrhage |
| ICP | intracranial pressure |
| ICU | intensive care unit |
| INCH | International Normalized Ratio (INR) Normalization in Coumadin Associated Intracerebral Hemorrhage |
| INR | international normalized ratio |
| INTERACT2 | The Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial |
| IPC | intermittent pneumatic compression |
| IVC | inferior vena cava |
| IVH | intraventricular hemorrhage |
| IVT | intraventricular thrombolysis |
| LMWH | low-molecular-weight heparin |
| LOE | Level of Evidence |
| LOS | length of stay |
| LVAD | left ventricular assist device |
| MIS | minimally invasive surgery |
| MISTIE III | Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation |
| MRA | magnetic resonance angiography |
| MRI | magnetic resonance imaging |
| mRS | modified Rankin Scale |
| MSU | mobile stroke unit |
| NCCT | noncontrast computed tomography |
| ND | neurological deterioration |
| NICE-SUGAR | Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation |
| NIHSS | National Institutes of Health Stroke Scale |
| NSAID | nonsteroidal anti-inflammatory drug |
| OR | odds ratio |
| PCC | prothrombin complex concentrate |
| PE | pulmonary embolism |
| PREVAIL | Evaluation of the WATCHMAN Left Atrial Appendage [LAA] Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy |
| PRoFESS | Prevention Regimen for Effectively Avoiding Second Strokes |
| PROGRESS | Perindopril Protection Against Recurrent Stroke Study |
| PROTECT-AF | WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation |
| QASC | Quality in Acute Stroke Care |
| RCT | randomized controlled trial |
| RRT | renal replacement therapy |
| RWI | relationships with industry and other entities |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SPARCL | Stroke Prevention by Aggressive Reduction in Cholesterol Levels |
| SSRIs | selective serotonin reuptake inhibitors |
| STICH | Surgical Trial in Intracerebral Hemorrhage |
| TBI | traumatic brain injury |
| TXA | tranexamic acid |
| UFH | unfractionated heparin |
| VKA | vitamin K antagonist |
| VTE | venous thromboembolism |

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## 2. GENERAL CONCEPTS

### 2.1. Small Vessel Disease Types

Despite our use of the term primary ICH to distinguish from ICH with a demonstrated structural cause (Section 1.4, Scope of the Guideline), these seemingly spontaneous hemorrhages are not truly primary but rather represent the consequence of defined underlying (and often co-occurring) vascular pathologies. The 2 common cerebral small vessel pathologies that account for the overwhelming majority of primary ICH are arteriolosclerosis and cerebral amyloid angiopathy (CAA). Each is a common age-related pathology, appearing at autopsy at moderate to severe extents in 30% to 35% of individuals enrolled in a longitudinal study of aging.[21] Arteriolosclerosis (also referred to as lipohyalinosis) is detected as concentric hyalinized vascular wall thickening favoring the penetrating arterioles of the basal ganglia, thalamus, brainstem, and deep cerebellar nuclei (collectively referred to as deep territories). Its major associated risk factors are hypertension, diabetes, and age. CAA is defined by deposition primarily of the β-amyloid peptide in the walls of arterioles and capillaries in the leptomeninges, cerebral cortex, and cerebellar hemispheres (lobar territories). The primary risk factors for CAA are age and apolipoprotein E genotypes containing the ε2 or ε4 alleles.

ICH occurs in a relatively small subset of those brains with advanced arteriolosclerosis or CAA, typically in deep territories for arteriolosclerosis and lobar territories for CAA,

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**Table 2. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)***

| CLASS (STRENGTH) OF RECOMMENDATION | |
|---|---|
| **CLASS 1 (STRONG)** | **Benefit >>> Risk** |
| **Suggested phrases for writing recommendations:**<br>• Is recommended<br>• Is indicated/useful/effective/beneficial<br>• Should be performed/administered/other<br>• Comparative-Effectiveness Phrases†:<br>– Treatment/strategy A is recommended/indicated in preference to treatment B<br>– Treatment A should be chosen over treatment B | |
| **CLASS 2a (MODERATE)** | **Benefit >> Risk** |
| **Suggested phrases for writing recommendations:**<br>• Is reasonable<br>• Can be useful/effective/beneficial<br>• Comparative-Effectiveness Phrases†:<br>– Treatment/strategy A is probably recommended/indicated in preference to treatment B<br>– It is reasonable to choose treatment A over treatment B | |
| **CLASS 2b (WEAK)** | **Benefit ≥ Risk** |
| **Suggested phrases for writing recommendations:**<br>• May/might be reasonable<br>• May/might be considered<br>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established | |
| **CLASS 3: No Benefit (MODERATE)**<br>**(Generally, LOE A or B use only)** | **Benefit = Risk** |
| **Suggested phrases for writing recommendations:**<br>• Is not recommended<br>• Is not indicated/useful/effective/beneficial<br>• Should not be performed/administered/other | |
| **Class 3: Harm (STRONG)** | **Risk > Benefit** |
| **Suggested phrases for writing recommendations:**<br>• Potentially harmful<br>• Causes harm<br>• Associated with excess morbidity/mortality<br>• Should not be performed/administered/other | |

| LEVEL (QUALITY) OF EVIDENCE‡ | |
|---|---|
| **LEVEL A** | |
| • High-quality evidence‡ from more than 1 RCT<br>• Meta-analyses of high-quality RCTs<br>• One or more RCTs corroborated by high-quality registry studies | |
| **LEVEL B-R** | **(Randomized)** |
| • Moderate-quality evidence‡ from 1 or more RCTs<br>• Meta-analyses of moderate-quality RCTs | |
| **LEVEL B-NR** | **(Nonrandomized)** |
| • Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies<br>• Meta-analyses of such studies | |
| **LEVEL C-LD** | **(Limited Data)** |
| • Randomized or nonrandomized observational or registry studies with limitations of design or execution<br>• Meta-analyses of such studies<br>• Physiological or mechanistic studies in human subjects | |
| **LEVEL C-EO** | **(Expert Opinion)** |
| • Consensus of expert opinion based on clinical experience | |

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

the brain locations favored by the underlying pathologies. Small, often asymptomatic cerebral microbleeds in these compartments are substantially more common, occurring in >20% of population-based individuals >60 years of age scanned with sensitive T2*-weighted MRI methods.[22,23] The presence of multiple strictly lobar ICHs, microbleeds, or cortical superficial siderosis (chronic blood products over the cerebral subpial surface) has been pathologically validated as part of the Boston criteria to detect CAA-related hemorrhage with reasonably high specificity and sensitivity.[24] Microbleeds associated with arteriolosclerosis tend to occur in deep territories but can appear in lobar territories as well.

The underlying small vessel types of ICH have several practical implications for the formulation of ICH guidelines. They establish a hemorrhage-prone environment in which use of antithrombotic agents creates increased risk of ICH.[25] It is important to note, however, that the small vessel pathologies that underlie ICH are also associated with increased risk of ischemic stroke,[26] highlighting the complexity and importance of balancing the risks versus benefits of antithrombotic treatment. Among the cerebral small vessel diseases, CAA inferred by the Boston criteria appears to confer substantially greater risk for recurrent hemorrhage than arteriolosclerosis (recurrent ICH rates in a pooled analysis of 7.39%/y after CAA-related ICH versus 1.11%/y after non–CAA-related ICH).[27]

## 2.2. Mechanisms for ICH-Related Brain Injury

ICH is understood to injure surrounding brain tissue through the direct pressure effects of an acutely expanding mass lesion and through secondary physiological

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and cellular pathways triggered by the hematoma and its metabolized blood products.[28] Direct pressure effects can include both local compression of immediately surrounding brain tissue and more widespread mechanical injury caused by increased intracranial pressure (ICP), hydrocephalus, or herniation. Early HE, possibly driven by mechanical shearing of surrounding vessels by the initial hematoma,[29] is common and a consistent predictor of worse ICH outcome.[30]

Secondary physiological and cellular injury mechanisms postulated to be triggered by ICH include cerebral edema, inflammation, and biochemical toxicity of blood products such as hemoglobin, iron, and thrombin.[28] Although it is plausible that the underlying small vessel disease type may affect the mechanism and severity of ICH-related brain injury, there is currently no strong evidence for substantial differences between the acute course of arteriolosclerosis-related and CAA-related ICH other than differences attributable to ICH location.

Several of the major medical therapies for ICH such as BP lowering and reversal of anticoagulation are aimed at limiting HE. The search for effective medical treatments for protecting tissue from secondary post-ICH injury, like the search for effective neuroprotectants for ischemic stroke, has to date been unsuccessful. Surgical hematoma evacuation through craniotomy, minimally invasive approaches, or ventriculostomy is aimed at both preventing further pressure-related injury and protecting against secondary physiological and cellular injury. One complexity that arises in the interpretation of results of surgical ICH trials is the possibility that mortality might be prevented without improvement in functional outcome, an issue addressed explicitly in the current guidelines.

## 2.3. Limits to Generalizability

A key limitation that runs through all sections of this guideline is that much of the data come from high-resource countries and from more affluent demographic groups within those countries. The potential limitations of generalizability to lower-resource settings and populations noted to be disproportionately at risk of ICH (Section 1, Introduction), highlight the need for future guidelines based explicitly on data from these underserved and underrepresented groups.

# 3. ORGANIZATION OF PREHOSPITAL AND INITIAL SYSTEMS OF CARE

**Recommendations for Organization of Prehospital and Initial Systems of Care**
**Referenced studies that support recommendations are summarized in Data Supplements 1 through 12.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. In patients with stroke, including spontaneous ICH, design and implementation of stroke public education programs for diverse populations focused on early recognition and the need to seek emergency care rapidly is useful to reduce time to diagnosis and treatment.[31–35] |

**Recommendations for Organization of Prehospital and Initial Systems of Care (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 2. In patients with sudden onset of neurological symptoms or signs attributable to potential spontaneous ICH, use of stroke recognition and severity tools is recommended for dispatch personnel and first responders to identify potential stroke and facilitate rapid transport to reduce time to diagnosis and treatment.[36–41] |
| 1 | B-NR | 3. In patients with stroke symptoms attributable to potential spontaneous ICH, immediate activation of the emergency response system (9-1-1 in North America) is recommended to reduce time to diagnosis and treatment.[32,42] |
| 1 | B-NR | 4. In patients with potential spontaneous ICH, early notification by emergency medical services (EMS) staff to the receiving hospital is recommended to improve time to diagnosis and treatment.[43,44] |
| 1 | C-LD | 5. In patients with spontaneous ICH, regional systems of stroke care are recommended so all potentially beneficial therapies can be made available when appropriate as rapidly as possible, including, at minimum, (a) health care facilities that provide initial spontaneous ICH care, including diagnosis and treatment, and (b) health care facilities with neurocritical care and neurosurgical capabilities.[45] |
| 2a | B-R | 6. In patients with potential stroke, including spontaneous ICH, in geographic regions where mobile stroke units (MSUs) operate, such mobile units are reasonable to enable more rapid diagnosis and treatment than achievable by ambulance transfer to the closest stroke-capable facility.[46,47] |
| 2a | C-LD | 7. In patients with potential spontaneous ICH, first responder training in stroke evaluation and care with the ability to provide airway and circulatory support when necessary is reasonable to detect and manage prehospital neurological deterioration (ND).[48,49] |

### *Synopsis*

Much of the data for prehospital care and stroke systems of care are derived from studies of stroke of all types (including ICH). Furthermore, it is generally not possible for prehospital clinicians to distinguish between patients with ICH and those with other types of stroke. As a result, the recommendations for prehospital care of patients with hemorrhagic stroke are essentially identical to those recommended for any patient with stroke: early recognition, expedient transport to the most appropriate facility, and prenotification before hospital arrival to expedite the in-hospital stroke response. Although it can be difficult to measure the precise time to onset of ICH treatment, it is reasonable to infer that earlier diagnosis will be closely linked to earlier treatment. To facilitate rapid diagnosis and treatment of ICH, we recommend public health measures to educate the public, build and maintain organized systems of care, and ensure appropriate training of first responders.

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## Recommendation-Specific Supportive Text

1. Early symptom recognition is essential for timely ICH care. In the United States, ≈67% of adults know the signs and symptoms of stroke and the need to call EMS; stroke knowledge increased almost 15 percentage points between 2009 and 2017.[33] Public education campaigns can improve stroke knowledge,[35,50] increase the use of EMS for stroke,[31] and use of EMS is associated with shorter time to diagnosis.[32] In the largest cluster randomized controlled study of >75 000 subjects, an educational intervention reduced time to hospital arrival in women (median, 328 minutes versus 559 minutes) but not men.[34] Although some smaller studies have demonstrated modest benefits, others have shown no or only transient benefits.[51–54] Knowledge of stroke warning signs varies by race, sex, ethnicity, age, education, and urbanicity,[33] which may contribute to disparities in outcomes. Public education campaigns should make every attempt to address underserved groups and those with the largest opportunities to improve awareness.
2. No existing clinical decision scale can differentiate ICH from other diseases with high sensitivity or specificity in the absence of neuroimaging. Prehospital scales such as FAST (Face, Arm, Speech, Time to call 911), LAPSS (Los Angeles Prehospital Stroke Scale), CPSS (Cincinnati Prehospital Stroke Scale), and ROSIER (Recognition of Stroke in the Emergency Room) are available and typically are validated in all stroke rather than ICH specifically.[41] Differences include whether they focus on sensitivity or specificity and whether they screen for stroke severity as well as presence. For dispatch, a group found that a specific dispatch stroke assessment tool was associated with shorter time to diagnosis,[37] and a clinical trial found that a dispatch stroke screen reduced time to both hospital arrival and stroke unit admission (although only 5% had ICH).[36] One group analyzed ICH specifically[39] and found an association between documented stroke scale use and ICH recognition. The sensitivity for ICH was 84%, and stroke scale documentation was independently associated with ICH recognition and shorter door–to–computed tomography (CT) times (20 minutes versus 47 minutes). Most studies of stroke scale use in practice inadequately account for false-negative cases, thereby likely artificially boosting performance. One group developed a clinical prediction rule to classify stroke subtypes, including ICH, in the prehospital setting; however, neither the sensitivity nor positive predictive value was published.[40]
3. One group found that in a large national cohort of patients with stroke, EMS use compared with arrival to hospital by other means is independently associated with earlier emergency department (ED) arrival (adjusted odds ratio [OR], 2.00 [95% CI, 1.93–2.08]), quicker ED evaluation (adjusted OR, 1.89 [95% CI, 1.78–2.00]), and more rapid treatment for ischemic stroke (adjusted OR, 1.44 [95% CI, 1.28–1.63]).[32,42] For ICH specifically, a large multicenter cohort study found that time from symptom onset to ED was 63 minutes versus 227 minutes in patients who used EMS versus those who did not use EMS, and time to hospital admission was 167 minutes versus 537 minutes.[55] Thus, persistent efforts to ensure activation of the 9-1-1 or a similar emergency system by patients or other members of the public for suspected stroke are warranted.
4. Many observational studies in patients with stroke (including both ischemic and ICH) have found that use of prehospital notification to the destination ED is associated with faster time to neuroimaging and shorter time to alteplase in ischemic stroke.[56–59] For example, a large registry found that after adjustment for covariates, EMS use (with prenotification) was associated with faster door-to-CT times than both private transport and EMS without prenotification.[44] In the AHA Get With The Guidelines–Stroke registry, EMS personnel provided prearrival notification to the destination ED for 67% of transported patients with stroke.[43] EMS prenotification was associated with shorter door-to-imaging times and shorter symptom onset–to–needle times. One group found that for ICH, early stroke team activation was associated with faster door-to-CT times (24 minutes versus 48 minutes) and faster time to hemostatic medication when used (63 minutes versus 99 minutes).[60]
5. Many regions have developed stroke systems of care and stratify hospitals according to their ability to deliver intravenous thrombolytics or endovascular therapy for ischemic stroke. Triage algorithms suggest routing patients on the basis of the results of prehospital stroke severity scales. These scales often indicate high severity in the case of ICH, which would direct patients with potential ICH preferentially to advanced stroke centers such as a comprehensive stroke center. Whether patients with ICH benefit from the higher level of care versus earlier temporizing at regional facilities remains to be seen and should be studied. One observational study found that Canadian provinces that had implemented stroke systems of care had reduced mortality for the entire cohort (including ICH, ≈10% of the cohort; adjusted incidence rate ratios, 0.85 [95% CI, 0.79–0.92]).[45]
6. Most studies of MSUs have focused on time to thrombolysis for stroke, and subgroup analyses of those diagnosed with ICH are small and underpowered. One group randomized their geographic region

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to weeks on/off for MSU availability and found that those patients treated in MSUs had faster times from symptom onset to laboratory results and to CT.[47] No MSU diagnosis of ICH (or lack of ICH) required revision during follow-up. Another study in 2 regions of Germany found similar reductions in time to CT.[46] The MSU reduced the use of interfacility transfer to zero for ICH because those with ICH were taken to a comprehensive stroke center as the initial hospital. Forty-one percent of the MSU patient group and none of the standard care group received BP management in the field after diagnosis, suggesting that MSU led to earlier initiation of treatment. Issues of logistics, feasibility, and cost currently appear to restrict MSU use to certain regions and facilities, and all studies are currently underpowered to evaluate any association with clinical outcome after ICH.

7. No clinical trials of different EMS response strategies were found to have been conducted in ICH. Some have been published in traumatic brain injury (TBI). One large clinical trial of TBI found that in patients with Glasgow Coma Scale (GCS) score <9, survival was lower in the advanced life support than basic life support stage.[49] In patients with TBI, it may be that prehospital intubation costs time that can outweigh any benefit and that bag-mask ventilation is adequate to both oxygenate and ventilate most patients during transport. Observational studies have noted that prehospital ND is relatively common after ICH.[48,61,62] This suggests a value for EMS clinicians trained in performing initial and serial neurological examinations using a stroke screening tool[63–66] and with the ability to provide expedient care, including airway support, for a patient who deteriorates during transport. Therefore, it is reasonable for advanced life support–trained clinicians to respond to patients with suspected stroke.

### *Knowledge Gaps and Future Research*

- Data on whether and what types of public health campaigns that help the public recognize stroke early translate into faster time to ICH diagnosis, treatment, and better outcomes are lacking. Future studies could ideally target which aspects of these campaigns are most useful in improving outcomes and in which populations.
- Data on which prehospital strategies translate to improved outcomes are limited; many studies are observational and confounded by local processes that select which teams go to which patients according to dispatch, severity, geography, and resources. Future studies may best target comparing a "scoop and run" approach (with minimal time/care on scene) to one sending a higher level of care (such as an MSU) to the scene. It is unknown whether prehospital basic life support or advanced life support yields better ICH outcomes. Data on the impact of MSUs on ICH are also limited.
- Much of the data for prehospital care and stroke systems of care were derived from studies of suspected stroke (including ICH), diagnosed stroke of all types (including ICH), or ischemic stroke. As a result, the recommendations for prehospital care are typically based on those for ischemic stroke or all strokes. Future research should evaluate whether particular systems of care are specifically beneficial to ICH, as well as the impact of regionalized large vessel occlusion stroke care on ICH outcomes and the impact of EMS bypass of primary stroke centers for suspicion of large vessel occlusion.
- Existing tools to stratify or diagnose ICH in the prehospital setting are limited. It remains unclear which, if any, tool is best or whether stroke scales that incorporate severity, rather than just stroke presence, are useful for ICH prehospital assessment. Further study of test characteristics of existing stroke severity scores in identifying patients with ICH is needed, whether the destination of patients with potential ICH should be the same as that for patients with large vessel occlusion strokes, or whether centers that do not have neurosurgical capabilities should be bypassed.
- Studies are needed to examine the potential benefit of mobile CT scanners to identify and treat ICH earlier. It will be important to determine whether other potential treatments targeted specifically to ICH improve outcome when provided earlier in the clinical course.

## 4. DIAGNOSIS AND ASSESSMENT

### 4.1. Diagnostic Assessment of Acute ICH Course

#### *4.1.1. Physical Examination and Laboratory Assessment*

**Recommendations for Physical Examination and Laboratory Assessment**
**Referenced studies that support recommendations are summarized in Data Supplement 13.**

| COR | LOE | Recommendation |
|---|---|---|
| 1 | C-LD | 1. In patients with spontaneous ICH, focused history, physical examination, and routine laboratory work and tests on hospital admission (eg, complete blood count, prothrombin time/international normalized ratio [INR]/partial thromboplastin time, creatinine/estimated glomerular filtration rate, glucose, cardiac troponin and ECG, toxicology screen, and inflammatory markers) should be performed to help identify the type of hemorrhage, active medical issues, and risk of unfavorable outcomes.[67–72] |

### *Synopsis*

Routine laboratory work provides important information about coagulation status and organ function that must be addressed rapidly in the setting of a spontaneous ICH (Table 3). A rapid assessment of laboratory data such as

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**Table 3. Initial History, Physical Examination and Laboratory Workup in Patients With ICH**

| Assessment type | Comments |
|---|---|
| History | |
| Time of symptom onset (or time patient was last normal) | |
| Symptoms | Headache<br>Thunderclap: Aneurysm, RCVS, some instances of CVST<br>Slower onset: Mass lesion, some instances of CVST, ischemic stroke with hemorrhagic transformation<br>Focal neurologic deficits<br>Seizures<br>Decreased level of consciousness |
| Vascular risk factors | Ischemic stroke<br>Prior ICH<br>Hypertension (Section 9.1.2)<br>Hyperlipidemia<br>Diabetes<br>Metabolic syndrome<br>Imaging biomarkers (eg, cerebral microbleeds; Section 9.1.1) |
| Medications | Antithrombotics:<br>Anticoagulants (Section 5.2.1), thrombolytics, antiplatelet agents (Section 5.2.2), NSAIDs (9.1.4), dose and time of last ingestion<br>Vasoconstrictive agents (associated with RCVS):<br>Triptans, SSRIs (Section 8.2), decongestants, stimulants, phentermine, sympathomimetic drugs<br>Antihypertensives (as a marker of chronic hypertension)<br>Estrogen-containing oral contraceptives (hemorrhage attributable to CVST) |
| Cognitive impairment or dementia | Associated with (but not specific for) amyloid angiopathy |
| Substance use (Section 9.1.5) | Smoking<br>Alcohol use<br>Marijuana (associated with RCVS)<br>Sympathomimetic drugs (amphetamines, methamphetamines, cocaine) |
| Liver disease, uremia, malignancy, and hematologic disorders | May be associated with coagulopathy |
| Physical examination | |
| Vital signs | Including assessment of airway, breathing, circulation |
| A general physical examination focusing on the head, heart, lungs, abdomen, and extremities | |
| A focused neurological examination | A structured examination (such as the NIHSS) can be completed in minutes and provides a quantification that allows easy communication of the severity of the event to other caregivers. GCS is relevant to patients with impaired level of consciousness. |
| Serum and urine tests | |
| Complete blood count, blood urea nitrogen and creatinine, liver function tests, glucose, inflammatory markers (ESR and/or CRP) | Anemia is associated with poor outcomes and hemorrhagic expansion.[73,74]<br>Thrombocytopenia is associated with increased mortality.[75]<br>Acute kidney injury and hyperglycemia are associated with worse outcomes and mortality.[68–71,76–81]<br>Inflammatory markers are associated with infective endocarditis.[82]<br>GFR influences clearance of DOACs.[83] |
| Prothrombin time (with INR) and an activated partial thromboplastin time, specific tests for DOACs when appropriate | Anticoagulant-related hemorrhages are associated with an increased hematoma volume, greater volume and time interval of expansion, and increased morbidity and mortality.[84–86]<br>Specific tests for DOACs (including dilute thrombin time, anti-Xa activity) may be useful for considering reanticoagulation.[87] |
| Cardiac-specific troponin and ECG | Elevated troponin levels are associated with increased mortality. Signs of left ventricular hypertrophy and other abnormalities on ECG can identify chronic hypertension, myocardial ischemia, or prior cardiac injury. |
| Urine toxicology screen | Cocaine and other sympathomimetic drugs are associated with ICH. |
| Pregnancy test in a woman of childbearing age | Peripartum angiopathy, eclampsia, HELLP syndrome, and sinus venous thrombosis can cause ICH in pregnant women. |

CRP indicates C-reactive protein; CVST, cerebral venous sinus thrombosis; DOAC, direct oral anticoagulant; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; GCS, Glasgow Coma Scale; GFR, glomerular filtration rate; HELLP, hemolysis, elevated liver enzymes, and low platelets; ICH, intracerebral hemorrhage; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; NSAID, nonsteroidal anti-inflammatory drug; RCVS, reversible cerebral vasoconstriction syndrome; and SSRI, selective serotonin reuptake inhibitor.

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complete blood count and coagulation profile can help to diagnose coagulopathy attributable to medications or underlying medical conditions such as hematologic malignancies.[72] This could lead to targeted therapies that can improve outcome. For surgical patients, coagulation status is important to determine whether external ventricular drainage (EVD) or craniotomy can be performed safely. Electrolyte disturbances, renal dysfunction, and acute cardiac syndromes can confound the clinical picture and require treatments that should be initiated urgently on hospital arrival.

### *Recommendation-Specific Supportive Text*

1. Complete blood count and coagulopathy studies (prothrombin time/partial thromboplastin time/INR) can help determine hemorrhage type, including spontaneous ICH attributable to extreme thrombocytopenia (eg, platelets <10 000, although platelet counts below higher thresholds also may contribute to ICH), anticoagulant-related hemorrhage, or coagulopathy secondary to malignancy or liver failure. Anticoagulant-related hemorrhages are associated with increased hematoma volume and expansion, as well as increased morbidity and mortality.[84–86] Admission anemia is associated with hemorrhagic expansion and poor outcomes[73,74] and thrombocytopenia is associated with higher mortality for patients taking antiplatelets.[75] In patients taking warfarin, admission INR value may predict outcome. One study showed a dose response of INR level in warfarin-related hemorrhage associated with poor outcome,[88] whereas another showed no association.[89] Elevated troponin on admission for patients with ICH is associated with increased in-hospital mortality for both medical and surgical ICH patient populations.[67,69,90–92] The association of admission troponin with functional outcomes and 30-day mortality was reported in 1 study[67] but not in another study after adjustment for confounding factors.[71] Renal failure on admission also is associated with poor functional outcomes,[71,76,77,79] in-hospital mortality,[80] and 12-month mortality.[76,79] Admission hyperglycemia is associated with unfavorable short- and long-term outcomes,[70] short-term mortality,[68,78,81] and long-term mortality after ICH.[68] Additional lifestyle risk factors that should be assessed include tobacco smoking, diet, alcohol, and waist-to-hip ratio.[93]

### *Knowledge Gaps and Future Research*

- Further studies are necessary to determine whether platelet or coagulation activity assays may identify a subgroup of patients who benefit from platelet transfusion, desmopressin acetate, tranexamic acid (TXA), or other acute therapies for ICH.
- Although changes in traditional coagulation factors or diluted thrombin time may indicate the presence of DOAC medications, these studies are not reliable enough to determine the level of anticoagulation at the time of presentation with DOAC-related ICH. Specific factor Xa inhibition levels have been developed for the factor Xa inhibitors and thrombin-based assays for dabigatran, but these studies are not widely available and often are not able to be run in an emergency setting quickly enough for decision-making. Specific reliable measurements of these anticoagulants could determine which patients may benefit from reversal of anticoagulation.
- Viscoelastic hemostatic assays, including thromboelastography and rotational thromboelastography, allow measurement of both cellular and plasma components of clot formation and fibrinolysis, unlike traditional coagulation tests (prothrombin time/partial thromboplastin time/INR) that reflect an in vitro coagulation pathway. These laboratory values predict significant bleeding and need for transfusions in trauma patients but have not been shown to improve outcome or mortality. Viscoelastic assays detect coagulation abnormalities that do not always appear on traditional coagulation tests in patients with ICH. It is unclear whether the results of these studies correlate with patient outcome. Understanding the significance of these studies in patients with ICH is an area of emerging and active research.
- Interpretation of admission ECG and troponin values can be challenging in patients with ICH because these can be either secondary to neurocardiogenic changes or attributable to true myocardial ischemia, which is important in the early evaluation and management of patients with ICH. Interpretation and management of early electrocardiographic changes in patients with ICH is an area of future study.

## *4.1.2. Neuroimaging for ICH Diagnosis and Acute Course*

**Recommendations for Neuroimaging for ICH Diagnosis and Acute Course**
**Referenced studies that support recommendations are summarized in Data Supplement 14.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients presenting with stroke-like symptoms, rapid neuroimaging with CT or MRI is recommended to confirm the diagnosis of spontaneous ICH.[94–96] |
| 2a | B-NR | 2. In patients with spontaneous ICH and/or IVH, serial head CT can be useful within the first 24 hours after symptom onset to evaluate for hemorrhage expansion.[97–99] |
| 2a | C-LD | 3. In patients with spontaneous ICH and/or IVH and with low GCS score or ND, serial head CT can be useful to evaluate for hemorrhage expansion, development of hydrocephalus, brain swelling, or herniation.[100–102] |

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| Recommendations for Neuroimaging for ICH Diagnosis and Acute Course (Continued) | | |
|---|---|---|
| COR | LOE | Recommendations |
| 2b | B-NR | 4. In patients with spontaneous ICH, CT angiography (CTA) within the first few hours of ICH onset may be reasonable to identify patients at risk for subsequent HE.[103–108] |
| 2b | B-NR | 5. In patients with spontaneous ICH, using noncontrast computed tomography (NCCT) markers of HE to identify patients at risk for HE may be reasonable.[106] |

### *Synopsis*

Brain imaging is essential to distinguish ICH from ischemic stroke and determine ICH volume (often estimated in practice with the ABC/2 formula[109]). CT is the most widely used imaging modality to confirm (or rule out) the presence of ICH because of its widespread availability, rapidity, high diagnostic accuracy, and ease. However, MRI with echo-planar gradient echo or susceptibility-weighted sequences also can detect hyperacute ICH with high accuracy.[94,95,110] Brain imaging during the acute phase of ICH can provide prognostic information and aid in monitoring the evolution of ICH. HE tends to occur early after ICH (typically within 24 hours of ICH onset) and is associated with poor outcome and mortality.[30,97,98,111] Identification of a spot sign on CTA or contrast-enhanced CT[104,107,108] or certain imaging features on NCCT such as heterogeneous densities within the hematoma or irregularities at its margins[106,112] may help to identify patients at risk for HE. These markers could influence the triage, monitoring intensity, and outcome prognostication for such patients. Repeating the CT after the initial scan to evaluate for development of HE, hydrocephalus, or perihematomal edema can be useful, particularly in patients whose neurological status deteriorates and in those with impaired level of consciousness in whom examination is limited.

### *Recommendation-Specific Supportive Text*

1. A prospective, multicenter, observational study of 62 patients presenting within 6 hours of spontaneous ICH reported that the sensitivity, specificity, predictive value, and accuracy of detecting ICH on MRI by experienced readers were 100%.[94] A similar study in 200 patients in which MRI was done first followed by CT found that MRI and CT were equivalent for detecting acute ICH and that MRI was more accurate for detecting chronic ICH.[95] A prospective, single-center study in patients with spontaneous ICH reported that MRI was slightly more sensitive than CT for detecting small IVH, where MRI sensitivity was 100% compared with 97% for CT.[96]
2. HE occurs early after ICH and is an independent predictor of ND, mortality, and poor functional outcome.[30,111] A prospective, observational study in 103 patients with spontaneous ICH who had a baseline CT within 3 hours of ICH onset and a repeat CT at 1 and 20 hours after baseline scan found that substantial HE occurred in 26% of patients on the 1-hour scans and in an additional 12% of patients on the 20-hour scans.[97] HE was associated with ND. In another study, the frequency of HE was greatest among those who underwent the initial CT scan within 3 hours of ICH onset and progressively declined as the time to initial scan was prolonged; 15% of patients exhibited HE between 6 and 12 hours and 6% between 12 and 24 hours. HE after 24 hours was extremely rare (0%).[98] However, delayed IVH has been reported in 21% of patients with no initial IVH, and infrequently beyond 24 hours,[99] delayed IVH is more likely to be associated with delayed HE, is independently associated with mortality and poor outcomes, and often requires emergency surgical intervention. Incorporating new IVH appearance and IVH expansion into the definition of HE appears to improve prediction of poor neurological outcome.[113,114] In patients with ICH with stable examination and preserved level of consciousness, follow-up CT scans at ≈6 and 24 hours after onset appear adequate to exclude HE and document final ICH volume.
3. This recommendation pertains to indications for repeat imaging to detect other downstream effects of recent hemorrhage that may occur beyond the first 24-hour period. Evidence derived from patients with mild TBI, defined as a GCS score ≥13, suggested that routine repeat head CT in neurologically stable patients is of low yield and often unnecessary,[100,115] whereas other evidence indicated that routine serial neuroimaging may have some value in patients with moderate or severe TBI.[101] However, these studies included few subjects with ICH (most patients had subarachnoid, subdural, or epidural hemorrhages), and the physiological differences between traumatic and nontraumatic hemorrhage limit the generalizability of these data to primary ICH. A single-center observational study in 239 patients with spontaneous ICH admitted to a neurological intensive care unit (ICU) with a standardized order set, including serial CT at 6, 24, and 48 hours and hourly neurological assessments, found that 35% of patients required emergency neurosurgical interventions after admission; 46% were instigated by imaging findings versus 54% by a change in neurological examination,[102] suggesting that routine serial imaging might be of supplemental value to neurological assessments. Beyond the first 24 hours, serial imaging is generally guided by the clinical picture of the patient.
4. Although benefits of therapies that target HE have currently not been demonstrated, stratification of patients

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at risk of HE can influence the triage and intensity of monitoring of these patients and their prognosis. A prospective, multicenter, observational study reported that HE was more frequent in patients with a CTA-positive spot sign than in those without it, although the negative and positive predictive values of the spot sign were not robust.[104] Mortality and poor modified Rankin Scale (mRS) score at 90 days were greater in patients with CTA-positive spot sign. Subsequent meta-analyses[106–108] also suggested that CTA-positive spot sign can predict HE and mortality, although interpretation of these analyses is limited by high heterogeneity of the included studies. A meta-analysis of individual data from 5435 patients reported that the addition of the spot sign provided small improvement in the discrimination of an HE prediction model composed of simple clinical variables (ICH volume, time from ICH onset to imaging, and use of antithrombotic drugs).[103] The sensitivity and positive predictive values of the spot sign to predict HE are time dependent; they are highest between 0 and 2 hours of ICH onset–to–scan time and decrease as time lapses.[105] CTA also can detect some structural causes of secondary ICH (Section 4.2, Diagnostic Assessment for ICH Pathogenesis). Although CTA does not appear to commonly trigger acute renal injury,[116] this risk remains a relevant consideration in obtaining this study.

5. Previous studies have suggested that signs on NCCT of heterogeneous density within the hematoma or irregularities at its margins (also described in the literature as hypodensities, fluid level, swirl, black hole, blend, island, or satellite signs) can serve as alternatives to the spot sign to predict HE[112] (Figures S1 and S2 in the Data Supplement). A meta-analysis of 25 studies including 10 650 patients reported that these NCCT markers are associated with HE and poor functional outcome, although there was substantial heterogeneity and pooled estimates were unadjusted for confounding variables.[106]

### *Knowledge Gaps and Future Research*

- Routine serial CT after the initial scan, regardless of neurological status, to evaluate for ICH expansion, development of hydrocephalus, or brain swelling is not uncommon in clinical practice. Although the usefulness of this practice has been studied extensively in patients with ICH attributable to TBI, there is a paucity of studies in patients with nontraumatic, spontaneous ICH. Future research should evaluate the cost/benefit implications of serial imaging after ICH and clarify the patient characteristics and conditions under which serial imaging should be considered.
- The utility of NCCT signs to predict HE, alone or as part of prediction scores based on clinical variables, and guide decision-making on the triage and monitoring of patients with ICH at high risk for HE is appealing, particularly in low-resource settings where immediate performance and interpretation of CTA are challenging. However, the prognostic yield and clinical relevance of these NCCT signs and scores are yet to be adequately examined in prospective large studies. An important goal of future research is to refine the utility of NCCT signs (defined by standardized criteria) and HE scores to maximize their diagnostic and predictive capabilities and validity.

## 4.2. Diagnostic Assessment for ICH Pathogenesis

**Recommendations for Diagnostic Assessment for ICH Pathogenesis Referenced studies that support recommendations are summarized in Data Supplement 15.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with lobar spontaneous ICH and age <70 years, deep/posterior fossa spontaneous ICH and age <45 years, or deep/posterior fossa and age 45 to 70 years without history of hypertension, acute CTA plus consideration of venography is recommended to exclude macrovascular causes or cerebral venous thrombosis.[117,118] |
| 1 | B-NR | 2. In patients with spontaneous IVH and no detectable parenchymal hemorrhage, catheter intra-arterial digital subtraction angiography (DSA) is recommended to exclude a macrovascular cause.[119] |
| 1 | C-LD | 3. In patients with spontaneous ICH and a CTA or magnetic resonance angiography (MRA) suggestive of a macrovascular cause, catheter intra-arterial DSA should be performed as soon as possible to confirm and manage underlying intracranial vascular malformations.[117,118,120–122] |
| 2a | B-NR | 4. In patients with (a) lobar spontaneous ICH and age <70 years, (b) deep/posterior fossa ICH and age <45 years, or (c) deep/posterior fossa and age 45 to 70 years without history of hypertension and negative noninvasive imaging (CTA±venography and MRI/MRA), catheter intra-arterial DSA is reasonable to exclude a macrovascular cause.[117,118,120–122] |
| 2a | B-NR | 5. In patients with spontaneous ICH with a negative CTA/venography, it is reasonable to perform MRI and MRA to establish a nonmacrovascular cause of ICH (such as CAA, deep perforating vasculopathy, cavernous malformation, or malignancy).[118,123,124] |
| 2a | C-LD | 6. In patients with spontaneous ICH who undergo CT or MRI at admission, CTA plus consideration of venography or MRA plus consideration of venography performed acutely can be useful to exclude macrovascular causes or cerebral venous thrombosis.[118] |
| 2b | C-LD | 7. In patients with spontaneous ICH and a negative catheter intra-arterial DSA and no clear microvascular diagnosis or other defined structural lesion, it may be reasonable to perform a repeat catheter intra-arterial DSA 3 to 6 months after ICH onset to identify a previously obscured vascular lesion.[125] |

### *Synopsis*

Heterogeneous disease entities such as arteriolosclerosis/lipohyalinosis, CAA, or vascular malformations may

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lead to acute brain parenchymal bleeding.[126] Clinicians should investigate the cause of ICH because it may influence acute and preventive treatment strategies and prognosis. Among individuals <70 years of age who did not have typical hypertension-related deep territory ICH, an underlying macrovascular cause (arteriovenous malformations, aneurysm, dural arteriovenous fistula, cavernoma and cerebral venous thrombosis) is present in 1 of 4 to 1 of 7 patients, depending on age category.[118] However, there is substantial heterogeneity in clinical practice in how, when, and in whom an underlying macrovascular cause is explored.[127] CTA and MRA appear to have >90% sensitivity and specificity after ICH for the detection of intracranial vascular malformations in highly selected populations compared with catheter intra-arterial DSA.[128] Catheter intra-arterial DSA remains the gold standard to search for macrovascular causes of ICH and appears to have the highest diagnostic yield as an adjunct or alternative to CT-based or magnetic resonance–based vascular imaging in (1) patients <70 years of age with lobar ICH, (2) patients <45 years of age with deep or posterior fossa ICH, (3) patients 45 to 70 years of age with deep or posterior fossa ICH and the absence of both history of hypertension and signs of small vessel disease on imaging, (4) all patients with ICH with CT or magnetic resonance evidence of a macrovascular lesion, and (5) patients with primary IVH.[117,118,120,129,130] CT or magnetic resonance venography should be included with CTA or MRA when clinical factors or ICH location suggests possible cerebral venous thrombosis.[131] For patients without evidence of macrovascular causes, MRI can be used to search for markers of ongoing diseases such as CAA, deep perforating vasculopathy, cavernous malformation, or malignancy.

### *Recommendation-Specific Supportive Text*

1. In the DIAGRAM (DIagnostic Angiography to Find Vascular Malformations) study, the median interval between NCCT and CTA was 1 day. In patients with lobar ICH and age <70 years, or deep/posterior fossa ICH and age <45 years, or deep/posterior fossa and age 45 to 70 years without hypertension, the diagnostic yield for diagnosis of a macrovascular cause was 17%. Hypertension was defined as history of hypertension, use of antihypertensive drugs before ICH, or evidence of left ventricular hypertrophy on admission ECG. None of the 291 patients had complications with CTA.[118] In multivariable analysis, younger age, location of ICH, absence of signs of small vessel disease (defined as presence of white matter lesions or a lacunar infarct in basal ganglia, thalamus, or posterior fossa, regardless of whether symptomatic or asymptomatic), and a positive or inconclusive CTA were independent predictors for the presence of an underlying macrovascular cause.[118] Estimated risks to identify a macrovascular cause varied from 1% in patients 51 to 70 years of age with deep ICH and signs of small vessel disease to >50% in patients 18 to 50 years of age with lobar or posterior fossa ICH and no signs of small vessel disease.[117]
2. Isolated IVH is a rare condition. In a single-center case series, 39 patients with isolated IVH were included during a 10-year period. In 30 patients, ≥1 angiographic examinations had been performed; 23% had an underlying macrovascular cause (arteriovenous malformation and dural arteriovenous fistula).[119] In a systematic review of the literature by the same authors, 16 studies reported 209 patients with isolated IVH. The yield of DSA was 58% (95% CI, 48%–68%) with large variations according to the design of the studies. Younger patients were more likely to have a macrovascular cause, but there was no influence of history of hypertension, small vessel disease, or anticoagulation use. There are currently insufficient data on the diagnostic yield of CTA or MRA for this purpose to know whether they provide equivalent diagnostic sensitivity.[119]
3. Identification of patients with underlying macrovascular lesions is important because lesions such as arteriovenous malformations and aneurysms are associated with potential rebleeding that should be prevented.[129,132] In addition to the characteristic appearances of macrovascular lesions on CTA and MRA, suggestive imaging findings can include CT demonstration of enlarged vessels or calcifications along the hematoma margins or hyperdensity within a dural venous sinus or cortical vein along the presumed venous drainage pathway of the hematoma.[120,129]
4. In the DIAGRAM study, DSA was assessed in 103 of 232 patients with negative or inconclusive CTA test results, of whom 97 also had negative or inconclusive MRI/MRA test results. The result of DSA was positive in 13%. The diagnostic yield for a macrovascular cause of combined CTA, MRI/MRA, and DSA was 23%. Complications with DSA resulting in permanent sequelae occurred in 0.6%.[118] In addition to the DIAGRAM score,[117] the simple ICH score[121] and secondary ICH score[120,129] have been developed to predict the probability of a macrovascular cause of ICH. The models incorporate a similar group of factors favoring further testing (CTA, MRI/MRA, or DSA): young age, lobar (or cerebellar) location, and absence of hypertension. The presence of small vessel disease on brain imaging also may be a useful variable associated with a lower likelihood of an underlying macrovascular cause.[122] Female sex was identified as a predictor of higher likelihood of a macrovascular

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lesion in the secondary ICH derivation study[120] but not in validation studies.[129,133]

5. MRI and MRA may provide valuable information on DSA-negative ICH causes (such as CAA, deep perforating vasculopathy, cavernous malformation, or malignancy).[123,124] Blood-sensitive T2*-weighted sequences should be included to detect brain microbleeds or cortical superficial siderosis that may contribute to discussions of the nature of the underlying vessel disease and of the prognostication of future ICH risk (Section 9.1.1, Prognostication of Future ICH Risk). Some 3-dimensional susceptibility-weighted sequences (eg, susceptibility-weighted imaging and susceptibility-weighted angiography) are particularly sensitive to these chronic hemorrhagic lesions. Contrast-enhanced T1-weighted MRI should be included to exclude neoplasm or other underlying mass lesion and is often repeated after 3 to 6 months for this purpose. In the DIAGRAM study, the median interval between CTA and MRI/MRA was 46 days. The diagnostic yield of combined CTA and MRI/MRA was 18%.[118] Both CTA and MRA appear to have good sensitivity and specificity after ICH for the detection of intracranial vascular malformations.[128] However, there is no head-to-head comparison to guide clinicians in their choice of imaging modality. The MRI approach will have the advantage of exploring both the detection of vascular malformations and giving clues on possible nonmacrovascular causes. Nonenhanced CT also can be used to detect ICH features suggestive of CAA such as subarachnoid extension or finger-like projects[134] or features of all small vessel diseases such as white matter hypodensity.
6. The rapid identification of any underlying intracranial vascular malformation (arteriovenous malformations, dural arteriovenous fistulae, and aneurysms) and of cerebral venous thrombosis is important and will influence treatment strategies and outcome.[118,135] The likelihood of identifying an underlying structural lesion appears to be somewhat lower in unselected patients with ICH than in those in one of the higher-risk categories listed in Recommendation 1 (lobar spontaneous ICH and age <70 years, deep/posterior fossa spontaneous ICH and age <45 years, or deep/posterior fossa and age of 45–70 years without a history of hypertension).
7. The concept of "primary" ICH or IVH is misleading. A thorough search for a cause should be performed and repeated if no definite microvascular or other structural cause is initially identified. This evaluation might include a second catheter intra-arterial DSA in patients with a low risk of complication. In a study of patients <65 years of age with subcortical ICH, 4 of the 22 who had a second catheter angiogram after an initial negative angiogram were found to have an arteriovenous malformation.[125]

### *Knowledge Gaps and Future Research*

- Diagnostic performance of noninvasive neuroimaging to disclose the underlying cause of the bleeding has been explored only in selected cohorts. For example, no data are available in people >70 years of age.
- Criteria to select people for further investigations would ideally not be based solely on the presence or absence of vascular risk factors such as hypertension or diabetes, which can be difficult to ascertain with certainty. In future studies, markers of small vessel disease (such as white matter hyperintensities, lacunes, microbleeds, or superficial siderosis) can increasingly be incorporated to classify people in high- or low-risk categories of underlying macrovascular lesions.
- Diagnostic criteria should be developed and validated to help clinicians and researchers to categorize people with ICH according to the cause of the bleeding. The presence or absence of risk factors does not definitively establish or preclude a specific ICH cause. Future diagnostic criteria might incorporate molecular fluid-based or imaging-based biomarkers such as β-amyloid.[136,137]
- Well-designed studies in nonselected populations should explore further whether DSA remains the gold standard to detect vascular malformations in patients with ICH at admission. Noninvasive imaging (including sequences such as arterial spin labeling or vessel wall imaging) could be useful in the future.
- Future clinical trials could be used to establish whether particular diagnostic strategies improve ICH outcome or recurrence risk.

## 5. MEDICAL AND NEUROINTENSIVE TREATMENT FOR ICH

### 5.1. Acute BP Lowering

**Recommendations for Acute BP Lowering**
**Referenced studies that support recommendations are summarized in Data Supplements 16 and 17.**

| COR | LOE | Recommendation |
|---|---|---|
| 2a | B-NR | 1. In patients with spontaneous ICH requiring acute BP lowering, careful titration to ensure continuous smooth and sustained control of BP, avoiding peaks and large variability in SBP, can be beneficial for improving functional outcomes.[138] |
| 2a | C-LD | 2. In patients with spontaneous ICH in whom acute BP lowering is considered, initiating treatment within 2 hours of ICH onset and reaching target within 1 hour can be beneficial to reduce the risk of HE and improve functional outcome.[139,140] |

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| Recommendations for Acute BP Lowering (Continued) | | |
|---|---|---|
| COR | LOE | Recommendations |
| 2b | B-R | 3. In patients with spontaneous ICH of mild to moderate severity presenting with SBP between 150 and 220 mm Hg, acute lowering of SBP to a target of 140 mm Hg with the goal of maintaining in the range of 130 to 150 mm Hg is safe and may be reasonable for improving functional outcomes.[138,141–147] |
| 2b | C-LD | 4. In patients with spontaneous ICH presenting with large or severe ICH or those requiring surgical decompression, the safety and efficacy of intensive BP lowering are not well established.[148] |
| 3: Harm | B-R | 5. In patients with spontaneous ICH of mild to moderate severity presenting with SBP >150 mm Hg, acute lowering of SBP to <130 mm Hg is potentially harmful.[146,149,150] |

### *Synopsis*

Most patients with acute ICH present with elevated BP. Elevated BP on presentation is associated with greater HE, ND, death, and dependency.[151–153] Therefore, it is intuitive to treat high BP during the acute phase of ICH. However, results from randomized clinical trials have been equivocal.[141,146] The current recommendations are based on data from the 2 largest trials (INTERACT2 [Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial] and ATACH-2 [Antihypertensive Treatment of Acute Cerebral Hemorrhage II]) for early intensive BP lowering (EIBPL) after ICH,[141,146] meta-analyses,[138,142,144,145,147] and several post hoc analyses of the INTERACT2 and ATACH-2 trials.[139,154,155] As a primary recommendation, lowering systolic BP (SBP) to a target range of 130 to 140 mm Hg is safe and may be reasonable in improving functional outcome in patients presenting with acute ICH of mild to moderate severity and SBP between 150 and 220 mm Hg. Initiating treatment as soon as possible and careful titration of BP-lowering therapy to ensure continuous smooth and sustained control of BP are recommended. Acute lowering of SBP to <130 mm Hg in patients presenting with ICH and elevated BP is potentially harmful and should be avoided.

### *Recommendation-Specific Supportive Text*

1. Several studies have shown that high SBP variability during the hyperacute and acute phases of ICH is associated with poor outcomes.[138,154,156] A post hoc analysis of INTERACT2 found that increased SD of SBP during the first 24 hours had a linear association with death and severe disability at 90 days.[154] A meta-analysis of INTERACT2 and ATACH-2 also showed a continuous association between achieved SBP and lesser variability during the first 24 hours after ICH and the distribution of mRS scores at 90 days, suggesting that avoiding large fluctuations in BP is beneficial.[138] There is a lack of evidence to guide the choice of BP-lowering agents during the hyperacute phase after ICH, including bolus versus drip management. Intravenous nicardipine was the drug used in ATACH-2, whereas a range of intravenous and oral BP-lowering agents were used in INTERACT2. Any antihypertensive drug with rapid onset and short duration of action to facilitate easy titration and sustained BP control to minimize SBP variability seems appropriate, although venous vasodilators may be harmful because of unopposed venodilation and its effect on hemostasis and ICP.[157]
2. The mean time from ICH onset to initiation of EIBPL treatment in ATACH-2 was 182±57 minutes compared with a median of 4 hours (interquartile range, 2.9–5.1 hours) in INTERACT2.[141,146] Evidence suggests that any potential benefit of BP lowering after ICH might be enhanced by earlier reductions in SBP. A subgroup analysis of ATACH-2 found that EIBPL within 2 hours of ICH onset was associated with lower risk of HE and improved 90-day outcomes compared with later time points.[139] In INTERACT2, reductions in SBP ≥20 mm Hg during the first hour after randomization and maintained for 7 days were associated with lowest risks of death and major disability.[140] Although the window for how long after ICH onset EIBPL remains beneficial has not been studied extensively, it would be expected to extend through the period when there is high risk for further HE.
3. EIBPL in patients with mild to moderate ICH (GCS score ≥5, excluding massive ICH) and SBP >150 to 220 mm Hg to 140 mm Hg appears to be safe. In INTERACT2, EIBPL to a target of 140 mm Hg with cessation of treatment at SBP <130 mm Hg was not associated with increased serious adverse events (SAEs) or mortality and resulted in modest improvement in secondary analyses of functional outcomes and quality of life domains but not in the primary outcome of death or major disability.[141] The mean minimum SBP in the EIBPL group was 150 mm Hg. In ATACH-2, EIBPL to a target of 110 to 139 mm Hg was not associated with a lower rate of death or disability compared with standard reduction to 140 to 179 mm Hg.[146] Another study using perfusion CT in patients with small to medium ICHs also found no significant reduction in cerebral blood flow within the perihematomal region with EIBPL to <150 mm Hg.[143] Several meta-analyses indicated that EIBPL is safe overall and not associated with increased risk for SAEs, severe hypotension, ND, or mortality.[138,142,144,145,147] A large systematic review and individual patient data meta-analysis including 16 randomized controlled trials (RCTs) with 6221 patients reported that EIBPL within 7 days of ICH onset reduced absolute and relative HE but did not improve functional outcomes.[158]

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Significant heterogeneity by BP-lowering strategy and agent was a limitation. Although patients with SBP >220 mm Hg were not intentionally included in the trials, it is common practice to take a similar BP-lowering approach in these patients.

4. A post hoc analysis of ATACH-2 trial of 682 participants with moderate to severe ICH (defined as GCS score <13, National Institutes of Health Stroke Scale [NIHSS] score ≥10, ICH volume ≥30 mL, or presence of IVH on presentation) found that EIBPL in this group reduced HE but did not reduce rate of death or disability at 90 days.[148] The safety of EIBPL and target BP for patients with large and more severe ICH and those requiring surgical decompression has less data. In patients with large ICH (>30 mL) requiring ICP monitoring or severe IVH requiring EVD, the burden of low cerebral perfusion pressure (CPP) <60 and <70 mm Hg was associated with increased mortality and poor functional outcomes, respectively, suggesting that BP reduction be accompanied by maintenance of CPP of 60 to ≥70 mm Hg in patients with large ICH, ICP elevation, or compromised CPP.[159,160]
5. Compared with INTERACT2, ATACH-2, which did not exclude patients with initial SBP >220 mm Hg, did not show added benefit by lowering SBP to 110 to 139 mm Hg. Although the SBP target of 110 to 139 mm Hg did not worsen neurological outcomes or increase mortality, the additional SBP reduction was associated with increased renal and SAEs during the follow-up period.[141,146] The mean minimum SBP for the EIBPL group in INTERACT2 was 150 mm Hg compared with 129 mm Hg in ATACH-2, implying that EIBPL to <130 mm Hg may negate potential benefits. This is consistent with a secondary analysis of INTERACT2[149] that showed that an achieved mean SBP <130 mm Hg was associated with a modest increase in physical dysfunction and that SBP of 130 to 139 mm Hg was associated with best outcomes and not influenced by baseline BP. Subsequent analysis of ATACH-2 data indicated that elevated baseline serum creatinine, ICH volume ≥25 mL, and higher doses of nicardipine were associated with increased risk for acute renal injury.[155] A post hoc analysis of ATACH-2 in participants with initial SBP ≥220 mm Hg (22.8% of the cohort) reported higher rates of ND at 24 hours and renal adverse events until day 7 or discharge in patients treated with EIBPL compared with standard BP lowering, without any benefit in reducing HE at 24 hours or death or severe disability at 90 days, suggesting that cautious BP lowering may be required in these patients.[150] Similarly, a prospective single-center cohort study of 448 patients with ICH determined that a threshold maximum SBP reduction of 90 mm Hg was significantly associated with acute kidney injury regardless of preexisting chronic kidney disease.[161] Acute kidney injury was associated with in-hospital mortality in patients with normal renal function but not in patients with chronic kidney disease.

### *Knowledge Gaps and Future Research*

- The safety and efficacy of EIBPL in patients with SBP >220 mm Hg and those with large and more severe ICHs, who may be more susceptible to cerebral perfusion compromise attributable to high ICP, require more study because these patients were not adequately represented in previous trials. There are insufficient data on which to base a target BP range for large ICH particularly in the absence of ICP monitoring. The rate of BP reduction in patients with excessively high SBP also requires additional study. In INTERACT2, ≈75% of patients presented with mild to moderate ICH <20 mL, median ICH volume was 11 mL, and NIHSS score was 10 in the EIBPL group. In ATACH-2, 91% of patients in the EIBPL group had an ICH volume <30 mL on presentation, median ICH volume was 10 mL, and NIHSS score was 11.
- Only 16% of patients in INTERACT-2 and 9.7% of patients in ATACH-2 had lobar ICH. More research is needed in the lobar subset of patients with ICH to address the different pathophysiology and natural history of lobar compared with deep ICH.
- It remains unclear whether ultraearly BP lowering could be beneficial. In RIGHT-2 (Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial), which included 145 of 1149 patients (13%) with ICH and SBP ≥120 mm Hg, transdermal nitroglycerine in the ambulance (median time from ICH onset to randomization, 74 minutes) was associated with worse outcomes and larger hematoma and edema volumes. Interpretation of these findings is limited by the small sample size and the potential confounding venous vasodilator effects of nitroglycerine and inhibition of the early vasoconstriction and platelet plugging phases of hemostasis on HE. The benefits of BP lowering beyond the first 6 hours after symptom onset also remain unclear because INTERACT2 and ATACH-2 required initiation of BP-lowering treatment within 6 and 4.5 hours of symptom onset, respectively.
- More research is also needed to better delineate the importance of various BP measures, including the selection and method (bolus versus drip) of administration of BP-lowering agent, absolute versus relative reduction, and prognostic significance of the magnitude of BP reduction during the first few hours. Secondary analyses of INTERACT2

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suggest that large SBP reductions >20 mm Hg within the first hour are associated with lower risks of poor outcomes at 90 days. In contrast, both the individual patient data analysis of INTERACT2 and ATACH-2 and a recent retrospective study in 757 patients found that early SBP reduction of >60 mm Hg in the first hour and between 40 and 60 mm Hg, respectively (compared with <20 mm Hg), were associated with an increased proportion of patients with unfavorable outcome, suggesting caution in lowering BP too quickly in patients with very high BP on arrival. These seemingly disparate findings merit further investigations. The most suitable target for BP reduction in untreated versus treated with controlled hypertension also warrants further exploration.

- Methods of BP measurement for early BP lowering after ICH have not been studied, including noninvasive versus invasive devices and frequency of measurements, which may be defined by studies evaluating targets for minimizing BP variability.

## 5.2. Hemostasis and Coagulopathy

### *5.2.1. Anticoagulant-Related Hemorrhage*

**Recommendations for Anticoagulant-Related Hemorrhage**
**Referenced studies that support recommendations are summarized in Data Supplements 18 and 19.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-LD | 1. In patients with anticoagulant-associated spontaneous ICH, anticoagulation should be discontinued immediately and rapid reversal of anticoagulation should be performed as soon as possible after diagnosis of spontaneous ICH to improve survival.[162] |
| VKAs | | |
| 1 | B-R | 2. In patients with VKA-associated spontaneous ICH and INR ≥2.0, 4-factor (4-F) prothrombin complex concentrate (PCC) is recommended in preference to fresh-frozen plasma (FFP) to achieve rapid correction of INR and limit HE.[163] |
| 1 | C-LD | 3. In patients with VKA-associated spontaneous ICH, intravenous vitamin K should be administered directly after coagulation factor replacement (PCC or other) to prevent later increase in INR and subsequent HE.[164,165] |
| 2b | C-LD | 4. In patients with VKA-associated spontaneous ICH with INR of 1.3 to 1.9, it may be reasonable to use PCC to achieve rapid correction of INR and limit HE.[162,164] |
| DOACs | | |
| 2a | B-NR | 5. In patients with direct factor Xa inhibitor–associated spontaneous ICH, andexanet alfa is reasonable to reverse the anticoagulant effect of factor Xa inhibitors.[166,167] |
| 2a | B-NR | 6. In patients with dabigatran-associated spontaneous ICH, idarucizumab is reasonable to reverse the anticoagulant effect of dabigatran.[168] |

**Recommendations for Anticoagulant-Related Hemorrhage (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | B-NR | 7. In patients with direct factor Xa inhibitor–associated spontaneous ICH, a 4-F PCC or activated PCC (aPCC) may be considered to improve hemostasis.[169–171] |
| 2b | C-LD | 8. In patients with dabigatran- or factor Xa inhibitor–associated spontaneous ICH, when the DOAC agent was taken within the previous few hours, activated charcoal may be reasonable to prevent absorption of the DOAC.[172–174] |
| 2b | C-LD | 9. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, aPCC or PCCs may be considered to improve hemostasis.[175,176] |
| 2b | C-LD | 10. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, renal replacement therapy (RRT) may be considered to reduce dabigatran concentration.[177] |
| Heparins | | |
| 2a | C-LD | 11. In patients with unfractionated heparin (UFH)–associated spontaneous ICH, intravenous protamine is reasonable to reverse the anticoagulant effect of heparin.[178] |
| 2b | C-LD | 12. In patients with low-molecular-weight heparin (LMWH)–associated spontaneous ICH, intravenous protamine may be considered to partially reverse the anticoagulant effect of heparin.[178] |

### *Synopsis*

The risk of HE, rapid deterioration, and poor outcome is increased in patients with ICH on anticoagulation therapy. Management requires emergency reversal of anticoagulation (Figure 2), and protocols and processes of care should be in place.

In general, treatment should be administered when clinically significant anticoagulant levels are suspected on the basis of type and timing of anticoagulant dosing rather than waiting for results of blood tests. Four-factor PCC is superior to plasma for warfarin-associated ICH to rapidly replace vitamin K–dependent coagulation factors[163] and should be given with intravenous vitamin K to re-establish vitamin K–dependent coagulation factor production. (Note that this guideline uses the term 4-F PCC when the supporting literature specifies this agent and otherwise uses the more general term PCC when the literature does not specify which PCC was used.) Reversal of the anticoagulant effect of direct thrombin inhibitors and factor Xa inhibitors can be performed rapidly with specific reversal agents (idarucizumab[168] and andexanet alfa,[166] respectively). However, there are few clinical data on the effectiveness of these agents in preventing HE or improving functional outcomes, and in real-world situations, clinicians will have to balance the expense against the benefit of these drugs. When specific reversal agents are not available, aPCC or 4-F PCC may promote hemostasis in patients on direct thrombin inhibitors[176]

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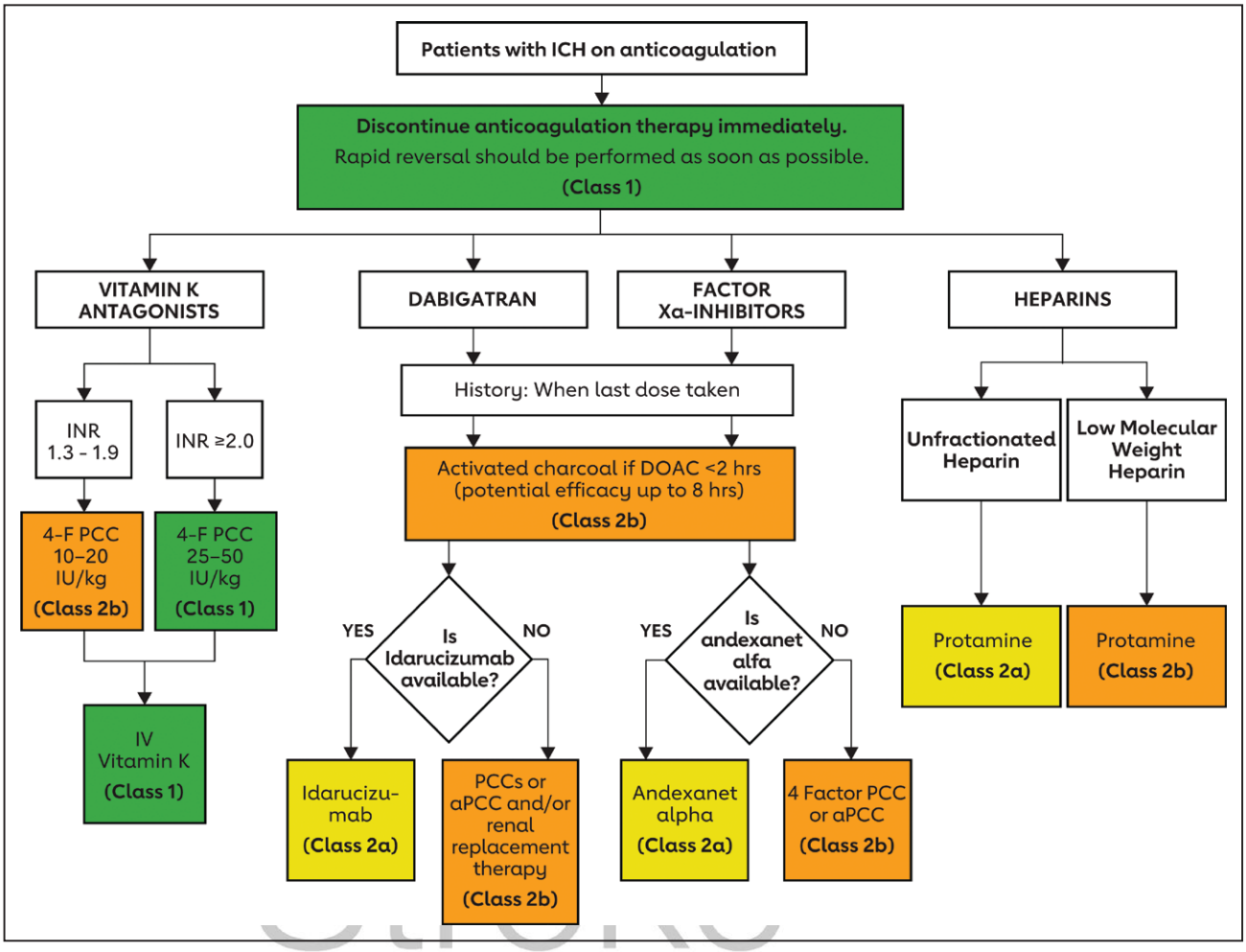


**Figure 2. Management of anticoagulant-related hemorrhage.**
aPCC indicates activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; INR, international normalized ratio; and PCC, prothrombin complex concentrate.

and factor Xa inhibitors.[169–171] RRT may reduce dabigatran concentration.[177] In patients on heparin, protamine reverses the anticoagulant effect.[178]

### *Recommendation-Specific Supportive Text*

1. In patients with anticoagulant-associated ICH and without preexisting limitation of life-sustaining therapies, the anticoagulant should be discontinued immediately and rapid reversal performed as soon as possible after diagnosis of ICH, regardless of whether the INR result is available. In a case series review of warfarin-related ICH, there were significant delays before administration of reversal therapy (mean, 3.3 hours from CT to PCC, 4.8 hours from arrival to reversal agent).[162] Earlier treatment was associated with a trend to better survival after controlling for severity (ICH score). In a large observational multicenter study, earlier (<4 hours) reversal of VKA-related ICH (to a goal INR <1.3) combined with BP control was associated with a significant reduction in HE and lower in-hospital mortality.[179] Time of last dose and renal function are likely to be the most useful tests to guide therapy; results of coagulation assays should not delay initiation of reversal therapy. Specific pathways may reduce time to reversal of anticoagulation. In 1 study, implementation of a bundle of care that included anticoagulation reversal, intensive BP lowering, neurosurgery, and access to critical care was significantly associated with lower 30-day mortality after ICH.[180] Reversal of anticoagulation in the presence of a left ventricular assist device (LVAD) does not appear to be associated with LVAD-related thrombosis on the basis of observational data.[181,182]
2. In an RCT comparing 4-F PCC 30 IU/kg with FFP in patients within 12 hours of onset of VKA-associated ICH and INR >1.9, 4-F PCC was superior at rapidly reversing anticoagulation (67% of 4-F PCC–treated patients achieved INR ≤1.2 within 3 hours of starting treatment versus 9% of FFP-treated patients).[163] In addition, 4-F PCC was associated with a reduction in HE (18.3% versus

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27.1% of FFP-treated patients at 24 hours). No statistically significant difference was observed in functional outcomes, although the study was not powered for this. The study was stopped early by the data safety monitoring board because of concerns in the FFP group, who had a higher rate of HE. There was no difference in SAEs or thromboembolic events. Infusion of PCC was significantly faster than infusion of FFP. An earlier RCT comparing 4-F PCC with FFP in patients with acute major bleeding and INR ≥2.0 included 24 patients with intracranial hemorrhage.[183] Overall, the study demonstrated noninferiority of 4-F PCC to FFP in hemostatic efficacy and superiority in rapid INR correction. The dose of 4-F PCC is based on INR and body weight (25–50 IU/kg), or fixed-dose regimens (1500 U for intracranial bleeding) are used.[87] The optimal dosing strategy will require large randomized studies. Although multiple formulations of both PCC and plasma products are available in different settings, most have not been systematically studied for their relative effectiveness.[87]

3. In a case review of 17 patients with VKA-associated major bleeding, PCC rapidly corrected the INR when given with or without vitamin K.[165] However, in 2 cases when PCCs were administered without vitamin K, despite initial rapid normalization of the INR, there was a rebound increase 12 to 24 hours later. One patient given PCC without vitamin K had hematoma enlargement with clinical deterioration. All participants in the INCH trial (International Normalized Ratio [INR] Normalization in Coumadin Associated Intracerebral Haemorrhage),[163] which confirmed the superiority of 4-F PCC over FFP, received 10 mg IV vitamin K in addition to 4-F PCC. Intravenous vitamin K at a dose of 5 to 10 mg should be administered regardless of the type of coagulation factor replacement (PCC or plasma) in patients with VKA-related ICH.[164]
4. Patients with VKA-associated ICH with INR <2.0 were excluded from the RCTs confirming superiority of PCC over FFP. A systematic review of the treatment of warfarin-associated bleeding included 318 patients in 12 studies, 3 of which included patients with intracranial hemorrhage. Patients who received PCCs had a more rapid correction of anticoagulation, but whether clinical outcomes were improved was unclear.[164] A case review of 88 patients with warfarin-related ICH and INR >1.2 demonstrated survival benefit of PCC over FFP.[162] Dosing information for 4-F PCC recommends doses for use only when INR ≥2.0. An observational study of 205 patients with VKA-related ICH treated with PCC to an INR ≥1.5 noted increased risk of venous thromboembolism (VTE) with higher doses of PCC (>2000 and 3000 IU).[184] Hence, a lower dose of 10 to 20 IU/kg is suggested when INR is <2.0 but ≥1.3 to achieve rapid correction of INR and limit HE.
5. Andexanet alfa is a recombinant coagulation factor that reverses the inhibition of factor Xa. In a large multicenter open-label study in patients with major bleeding within 18 hours after administration of a factor Xa inhibitor (apixaban, edoxaban, enoxaparin, rivaroxaban), andexanet alfa significantly reduced anti–factor Xa activity, with a 10% VTE rate and 15% mortality rate.[166] In a subgroup publication of patients with factor Xa inhibitor–associated ICH, excellent or good hemostatic outcome, defined as <35% increase in hematoma volume after 12 hours, was seen in 79% of patients.[167] A number of small single-center case series have described comparable rates of hemostatic efficacy, mortality, and safety comparing andexanet alfa with PCC, although definitions of HE vary.[185] Data comparing outcomes in patients given either andexanet alfa or PCC are limited by baseline imbalances between the groups attributable to selection bias. In a small single-center study, higher rates of hemostatic efficacy and thromboembolism were seen in the andexanet alfa group, and cost was significantly higher when andexanet alfa was used compared with PCC.[186] In another small comparison, andexanet alfa was similar to PCC in terms of stability of hematoma on CT at 6 and 24 hours.[187] Hence, although andexanet alfa can be effective to reverse anti–factor Xa activity, data on safety and clinical outcomes (including functional outcome) from a randomized trial are awaited. Because of the structural similarity of the factor Xa inhibitors, andexanet alfa also likely neutralizes betrixaban and edoxaban in the same manner.[188] The recommended dosing of andexanet alfa depends on the specific factor Xa inhibitor and the time since last dose.[189]
6. Idarucizumab, a monoclonal antibody, binds dabigatran with high affinity and neutralizes its activity. In a large prospective cohort study, in patients taking dabigatran with serious bleeding or undergoing a procedure, including 53 patients with ICH, idarucizumab 5 g (administered as two 2.5-g boluses) rapidly led to complete reversal of dabigatran (based on diluted thrombin time or ecarin clotting time) independently of age, sex, and renal function, with thrombotic events occurring in 5% of the patients with ICH.[168,190] Unfortunately, imaging studies were not mandated in the ICH populations, and there are no data on clinical outcomes in the ICH population except that 17% of the patients with ICH died within the first 5 days. A number of real-world case series in both the United States[191] and Europe[175,192,193] have shown similar rates of

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mortality and acceptable incidence of thrombotic events, suggesting a therapeutic effect of idarucizumab after ICH. The absence of a control group and lack of imaging data limit any conclusions on clinical efficacy.

7. In healthy volunteers taking factor Xa inhibitors at doses of 37.5 to 50 IU/kg, 4-F PCC reverses coagulation assays.[194–198] A meta-analysis of 10 single-arm case series included 251 patients with factor Xa inhibitor–related ICH given 4-F PCC. Effective hemostasis was seen in most cases with acceptable mortality rates and thrombosis risk.[171] In a multicenter observational study including 172 patients with factor Xa inhibitor–related ICH given 4-F PCC or aPCC, a high rate of hemostasis and low risk of thrombotic events (5% with aPCC, 3.3% with 4-F PCC) were seen.[170] In another multicenter retrospective case series, there were no differences in efficacy, mortality, or safety with aPCC and both low- and high-dose 4-F PCC in patients taking apixaban or rivaroxaban presenting with ICH.[169] In another case series, although factor Xa levels on admission were associated with HE, administration of PCC was not associated with differences in HE, mortality, or functional outcomes.[199] aPCC and 4-F PCC have not been directly compared in a randomized trial for factor Xa inhibitor reversal, although there is more evidence from observational studies to support the use of 4-F PCC, which is also more widely available.
8. In a preclinical in vitro study, adsorption of dabigatran by activated charcoal removes dabigatran from pooled human plasma.[173] It is advised that charcoal should be given within 2 hours of ingestion before intestinal absorption of dabigatran. In healthy volunteers given activated charcoal 2 and 6 hours after apixaban ingestion, apixaban absorption was reduced and half-life was significantly reduced.[174] Similarly, activated charcoal given to healthy volunteers up to 8 hours after ingestion of rivaroxaban significantly reduced exposure.[172] Thus, activated charcoal is a supplementary treatment option in DOAC-associated ICH when the most recent dose was taken within the previous 2 to 8 hours in order to enhance elimination and neutralize the ongoing anticoagulant effect. Only single case reports exist in patients with hemorrhage, so it is not possible to comment on clinical outcomes.
9. In a prospective multicenter case series, 5 patients with dabigatran-associated ICH bleeding treated with aPCC (FEIBA, 50 U/kg) were compared with matched cases receiving supportive care. Patients treated with aPCC had favorable outcomes compared with the matched control subjects as assessed by treating physicians with no thromboembolic events.[176] In a small single-center retrospective case series, aPCC (FEIBA) was given to 16 patients with dabigatran-associated bleeding; no clinically significant HE was observed.[175] These case series, although small and limited by lack of control, suggest that aPCC can reverse dabigatran and may be considered when idarucizumab is not available. In vitro thrombin generation studies show that PCCs increase peak thrombin generation with variable effects on kinetic parameters and suggest that PCC at a dose of 50 IU/kg can produce hemostasis at therapeutic dabigatran levels.[200] However, in healthy volunteers treated with DOACs, reversal with procoagulant concentrates (PCC or aPCC) did not fully restore levels of fibrin formation in studies with flowing blood, especially for dabigatran, suggesting potential limitations of the nonspecific PCC strategies to reverse DOAC-induced coagulopathy.[201,202]
10. Dabigatran is excreted by the kidneys, and elimination is delayed in those with renal impairment. Therefore, RRT is able to decrease the plasma concentrations of dabigatran, although the effect of RRT on clinical outcomes is unclear. In a systematic review of the literature, including 11 patients with ICH who underwent RRT for dabigatran removal, patients had normal renal function or varying degrees of renal impairment. RRT in the form of hemodialysis (intermittent hemodialysis in 10 patients, continuous veno-veno hemodialysis in1 patient) was effective at reducing dabigatran concentrations. The majority of patients received PCC in addition to RRT. Recovery or rehabilitation was reported in the majority of patients, but a quarter died as a result of progression of intracranial bleeding. Half the patients had rebound of dabigatran concentrations after cessation of RRT.[177]
11. Protamine binds to UFH and thus neutralizes the anticoagulant effect of UFH. Hence, in patients with UFH-associated ICH, intravenous protamine is reasonable to reverse the anticoagulant effect of heparin.178 However, because UFH has a short half-life and protamine can cause hypersensitivity reactions and is a weak anticoagulant, caution is needed in the selection of the required dose.[203] Intravenous protamine should not exceed 50 mg/10 min because of the risk of hypotension and bronchoconstriction; repeated smaller doses are preferable.[178]
12. In a small retrospective case series of patients on LMWH, protamine only partially reversed the anticoagulant effect. The majority of patients had cessation of bleeding. Protamine only partially affected anti–factor Xa levels, which were of use to assess the amount of anticoagulant present but did not predict the effect of protamine.[204] Therefore, intravenous protamine is reasonable to partially reverse the anticoagulant effect of LMWH.[178] Andexanet alfa has also been shown to significantly reduce anti–factor Xa levels in 16 patients taking enoxaparin.[166]

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### Knowledge Gaps and Future Research

- Hemostatic expansion remains a therapeutic target after ICH. There is a lack of data on the clinical benefit of reversal of anticoagulation (eg, HE, functional outcome) compared with confirmation of reversal of anticoagulation parameters.
- The clinical utility of anticoagulant tests for the DOACs is not established. The role of blood tests (eg, anticoagulant parameters, thromboelastography, point-of-care tests) to target reversal of anticoagulation therapy should be studied.
- Choice of reversal agents for anticoagulation therapy-related ICH will continue to evolve as our understanding of efficacy, safety, and thromboembolic risk is better defined. Development and research of new anticoagulant reversal agents is encouraged. One new agent, ciraparantag (aripazine), is designed to be a universal antidote to factor Xa inhibitors, dabigatran, LMWH, and UFH.[205] Phase II and III clinical trials are awaited.
- There are limited data on when to administer idarucizumab relative to last dose of dabigatran and on the use of idarucizumab with PCCs and other blood products. Rapid hemostasis may not be ensured in patients with existing comorbidities or hypocoagulable states that impair clotting.
- The potential synergistic benefits of a bundle of care, including BP lowering and reversal of anticoagulation, should be studied, as well as specific care pathways (eg, keeping reversal agents on the ward, not requiring consultation with hematology, training of nurses). Such pathways may reduce time to reversal of anticoagulants and improve outcome.

### 5.2.2. Antiplatelet-Related Hemorrhage

**Recommendations for Antiplatelet-Related Hemorrhage**
**Referenced studies that support recommendations are summarized in Data Supplements 20 through 25.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | C-LD | 1. For patients with spontaneous ICH being treated with aspirin and who require emergency neurosurgery, platelet transfusion might be considered to reduce postoperative bleeding and mortality.[206] |
| 2b | C-LD | 2. For patients with spontaneous ICH being treated with antiplatelet agents, the effectiveness of desmopressin with or without platelet transfusions to reduce the expansion of the hematoma is uncertain.[207–209] |
| 3: Harm | B-R | 3. For patients with spontaneous ICH being treated with aspirin and not scheduled for emergency surgery, platelet transfusions are potentially harmful and should not be administered.[210] |

### Synopsis

The effect of antiplatelet agents on the outcome of ICH is uncertain. A systematic review of 25 observational studies found that antiplatelet therapy at the time of the hemorrhage was associated with a 27% increase in mortality but not with functional outcome.[211] In a more recent retrospective cohort study with 3545 patients, antiplatelet use on its own was not independently associated with worse functional outcome, whereas when an antiplatelet was combined with a VKA, there was a reduced chance of favorable outcome, as defined by an mRS score of 0 to 3.[212] In an RCT, the subset of patients with antiplatelet therapy had more unfavorable functional outcome and higher mortality.[213] The studies generally do not provide separate results for different antiplatelet agents, which vary in terms of degree of platelet inhibition, half-life, and reversibility. Platelet transfusions, desmopressin, and TXA have proven effective in reducing bleeding in other clinical indications,[214–216] whereas for spontaneous ICH in patients being treated with antiplatelet agents, no convincing benefit has been demonstrated.[207–210,213] The exception is emergency craniotomy for hematoma removal, for which reversal of the antiplatelet effect of aspirin with platelet transfusions might reduce postoperative hemorrhage volume.[206]

### Recommendation-Specific Supportive Text

1. One moderate-size RCT studied patients with acute hypertensive basal ganglia hemorrhage and requiring emergency craniotomy for removal of the hematoma who were also receiving aspirin therapy. Results showed that transfusion of 1 U of previously frozen apheresis platelets before surgery, with or without an additional platelet unit 24 hours later, reduced postoperative rate and volume of hemorrhage.[206] Platelet transfusion also was associated with higher activities of daily living (ADL) score and lower 6-month mortality. All patients screened were investigated with a platelet aggregation test to exclude those with aspirin resistance. The excluded patients did not receive platelet transfusions; however, their outcomes were similar to those of patients with sensitivity to aspirin and treated with platelet transfusions. Among the methodological limitations of this trial, SAEs were not reported in this population, cases with incomplete hemostasis during operation were excluded, nonuniform surgical procedures were performed, and the methodology of ICH volume determination was below the current standard. Platelet aggregation testing is rarely available on an emergency basis in clinical practice.
2. In 2 retrospective studies in patients with spontaneous ICH while taking antiplatelet agents,[207,209] treatment with desmopressin (0.3 μg/kg) was associated with reduced expansion of the hematoma in 1 of the studies.[207] The latter study

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included all ICHs, of which 42% were intraparenchymal, but results were not provided for the subsets. In a third retrospective study in patients with spontaneous ICH while on antiplatelet agents, treatment with desmopressin (0.4 μg/kg) in combination with platelet transfusion did not reduce HE or improve functional outcome compared with usual care.[208]

3. A moderate-size RCT in patients with spontaneous supratentorial ICH and concomitant antiplatelet therapy who were not planned for surgical evacuation showed that 1 U platelet concentrate (2 U for adenosine-diphosphate receptor blockers) given for the purpose of reducing HE and thereby reducing death or dependence was associated with a shift toward worse functional outcome at 3 months, as measured with the mRS, and a borderline significant increase in risk of any SAE.[210] There was no reduction in the expansion of the intracerebral hematoma or in 3-month mortality. Although this study was open to enrollment of individuals taking either cyclooxygenase inhibitors (such as aspirin) or ADP receptor blockers (such as clopidogrel), only 5 of the 190 participants were taking ADP blockers alone, limiting the generalizability of the findings to antiplatelet agents other than aspirin. These findings do not apply to preoperative platelet transfusions.

### Knowledge Gaps and Future Research

- Studies of antiplatelet-related ICH have mostly included only aspirin. It will be important to study the effects of reversal of other antiplatelet agents, especially the ADP receptor P2Y12 inhibitors.
- Platelet transfusions appear beneficial for reversal of aspirin before craniotomy and hematoma evacuation, but it is not known whether this effect also pertains to other invasive procedures or surgeries such as EVD and minimally invasive surgery (MIS).
- The apparent beneficial effect of platelet transfusions for reversal of aspirin before craniotomy in a Chinese population should be confirmed in other populations with rigorous volumetric data and with adverse event reporting.
- The effect of desmopressin is uncertain because of the lack of RCTs, but such trials are ongoing.
- Ticagrelor is not reversed by platelet transfusions. A monoclonal antibody against ticagrelor reversed inhibition of platelet function in healthy volunteers.[217] A phase III trial to evaluate the clinical effectiveness of this antidote is ongoing.

## 5.2.3. General Hemostatic Treatments

**Recommendations for General Hemostatic Treatments**
**Referenced studies that support recommendations are summarized in Data Supplements 26 and 27.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | B-R | 1. In patients with spontaneous ICH (with or without the spot sign), the effectiveness of recombinant factor VIIa to improve functional outcome is unclear.[218,219] |
| 2b | B-R | 2. In patients with spontaneous ICH (with or without the spot sign, black hole sign, or blend sign), the effectiveness of TXA to improve functional outcome is not well established.[220–222] |

### Synopsis

HE occurs in up to a third of patients after ICH and is associated with poor outcome.[103] Hemostatic therapy for the prevention of HE remains an attractive therapeutic target after ICH. To date, large RCTs have assessed 2 agents, recombinant factor VIIa and TXA. The modest effects of these agents on limiting HE have not translated into improvement in functional outcome. Presence of the CTA spot sign or other CT indications of possible HE did not predict beneficial response to either hemostatic therapy. ICH expansion most commonly occurs very early after onset, and future studies need to target earlier treatment.

### Recommendation-Specific Supportive Text

1. Numerous phase II dose escalation and pilot studies have been performed testing recombinant factor VIIa.[223–226] In a phase IIb RCT, a dose-dependent reduction in HE and significant reduction in poor functional outcome were seen with recombinant factor VIIa. There was no difference in serious thromboembolic events.[219] However, in a larger phase III study testing recombinant factor VIIa within 4 hours of ICH onset, despite significant similar modest limitation of HE with the 80–μg/kg dose, there was no difference in functional outcome at 3 months compared with placebo. There was a significant increase in arterial thrombotic events.[218] Meta-analysis of recombinant factor VIIa RCTs showed no benefit on HE, functional outcome, or SAEs.[227] However, a secondary post hoc analysis found trends toward improved outcome with recombinant factor VIIa treatment among younger patients with ICH with smaller hematoma volumes and shorter onset-to-treatment intervals,[228] raising the possibility that future studies might identify meaningful patient subgroups for treatment. In a pooled analysis of 2 RCTs that were halted early after they failed to achieve recruitment targets, the use of the CTA spot sign was not effective in predicting response to factor VIIa 80 μg/kg given within 6.5 hours of ICH onset, and

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there was no difference in expansion or functional outcome between the treatment groups.[229]

2. In a large phase III RCT, TXA led to a significant but modest reduction in HE and early death (within 7 days) but no significant difference in functional outcome.[222] TXA was safe with no increase in VTE and a reduction in SAE compared with placebo. The study had an 8-hour time window, and most patients were enrolled >3 hours after ICH onset. There was a significant interaction with baseline SBP, showing a favorable shift in outcome with TXA in participants with baseline SBP <170 mm Hg. In 2 small phase II trials in patients with positive CTA spot sign and including black hole sign and blend sign in 1 trial, there was no significant difference in HE or functional outcome at 3 months.[220,221] In a recent meta-analysis including these 2 RCTs, TXA demonstrated a reduction in HE predicted by markers on CT scan but no difference in mortality or functional outcome.[230]

### *Knowledge Gaps and Future Research*

- The time window for administration of hemostatic therapies remains uncertain. Specifically, it will be important to determine whether rapid administration of hemostatic therapy (such as recombinant factor VIIa or TXA) limits HE, reduces mortality, and improves functional outcome. Larger trials of these hemostatic therapies with earlier treatment windows are underway.
- Another important goal is to identify patients at risk of HE (with factors other than time) who may still have the potential to benefit from hemostatic therapies. This could potentially include imaging markers to predict HE (eg, spot sign, blend, black hole sign) or other imaging factors (IVH, volume) or blood tests (eg, thromboelastography, glial fibrillary acidic protein) to select patients most likely to benefit from hemostatic therapies.
- It is unknown if there is an ICH volume threshold above which limiting HE does not translate into clinical benefit.
- Another important knowledge gap is determining if there is a potential synergistic effect of combined BP lowering and hemostatic therapy.

## 5.3. General Inpatient Care

### *5.3.1. Inpatient Care Setting*

**Recommendations for Inpatient Care Setting**
**Referenced studies that support recommendations are summarized in Data Supplements 28 and 29.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with spontaneous ICH, provision of care in a specialized inpatient (eg, stroke) unit with a multidisciplinary team is recommended to improve outcomes and reduce mortality.[231,232] |

**Recommendations for Inpatient Care Setting (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 2. In patients with spontaneous ICH, provision of care at centers that can provide the full range of high-acuity care and expertise is recommended to improve outcomes.[233] |
| 1 | B-NR | 3. In patients with spontaneous ICH and clinical hydrocephalus, transfer to centers with neurosurgical capabilities for definitive hydrocephalus management (eg, EVD placement and monitoring) is recommended to reduce mortality.[233,234] |
| 1 | C-LD | 4. In patients with spontaneous ICH, care delivery that includes multidisciplinary teams trained in neurological assessment is recommended to improve outcomes.[99,235,236] |
| 1 | C-EO | 5. In hospitalized patients with spontaneous ICH who require hospital transfer but do not have adequate airway protection, cannot support adequate gas exchange, and/or do not have a stable hemodynamic profile, appropriate life-sustaining therapies should be initiated before transportation to prevent acute medical decompensation in transport. |
| 2a | B-NR | 6. In patients with spontaneous ICH without indications for ICU admission at presentation, initial provision of care in a stroke unit compared with a general ward is reasonable to reduce mortality and improve outcomes.[231,237,238] |
| 2a | B-NR | 7. In patients with moderate to severe spontaneous ICH, IVH, hydrocephalus, or infratentorial location, provision of care in a neuro-specific ICU compared with a general ICU is reasonable to improve outcomes and reduce mortality.[235,239–241] |
| 2b | B-NR | 8. In patients with IVH or infratentorial ICH location, transfer to centers with neurosurgical capabilities might be reasonable to improve outcomes.[102,233,234] |
| 2b | C-LD | 9. In patients with larger supratentorial ICH, transfer to centers with neurosurgical capabilities may be reasonable to improve outcomes.[233,234] |

### *Synopsis*

Patients with ICH who have clinical hydrocephalus, IVH, or infratentorial hemorrhage are best cared for in facilities with neurosurgical and neuro-specialized critical care capabilities. It can be challenging to predict a priori which of these subsets of patients with ICH will require neurosurgical evaluation or management. Therefore, treatment facilities without in-house access to neurosurgical and neurocritical care capabilities should ensure the ability to obtain a consultation for such care or consider transfer to facilities that have these resources. The present guideline recommends that appropriate life-sustaining therapies be initiated before transfer for patients with ICH with an unstable hemodynamic profile, inadequate airway protection, or inadequate gas exchange. Recommendations are intended for patients with no limitation of life-sustaining therapy, the initiation of which should be consistent with the patient's advance directive information and goals of care. A do not attempt resuscitation (DNAR) order does not itself indicate that the patient

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should not receive emergency treatment (Section 7.2, Decisions to Limit Life-Sustaining Treatment). Determination of the optimal timing for patients with ICH to transition from the ED to another care environment such as an ICU is complex and may be related to the ability for that ED to manage critically ill patients.[242,243] Depending on the severity of hemorrhage, the appropriate inpatient setting may be an ICU (defined by provision of the full spectrum of critical care and intensive monitoring) or a dedicated stroke unit (licensed by regional or national stroke organizations according to standard of care and round-the-clock stroke expertise).

### *Recommendation-Specific Supportive Text*

1. ICH is a complex clinical event that has been shown to benefit from specially trained, multidisciplinary care. Meta-analysis has shown the benefit of dedicated care such as a stroke unit for both ischemic stroke and ICH. The benefits of multidisciplinary care likely relate to the complex and multifaceted clinical domains affected by ICH. Rehabilitation teams and specially trained nurses working together with physicians familiar with patients with ICH have been shown to improve outcomes and reduce mortality compared with a general medical ward.[231,232]
2. In patients with ICH, initiating coagulopathy reversal and BP control before transfer is recommended to avoid delays in treatment.[233] However, in cases when transfer is the priority according to clinical assessment, it is best not to delay transfer. A study bundled BP control and correction of coagulopathy among other care initiatives and achieved improvement in early delivery of intensive BP lowering, although no significant change in time to reversal of coagulopathy was achieved. Bundled care did improve 30-day survival, which was mediated predominantly by a decrease in DNAR orders and increased admission to the ICU, both of which are likely to improve attainment of anticoagulation reversal and BP lowering.[233]
3. Determining whether enlarged ventricles represent ICH/IVH–related hydrocephalus versus unrelated conditions such as central brain atrophy can be challenging. Furthermore, some patients with ICH with expansion of the ventricles will require ventriculostomy, whereas others may not. Clinical hydrocephalus, defined as a worsening clinical examination attributable to acute hydrocephalus from ICH, is associated with worsened prognosis.[244] Patients who develop clinical hydrocephalus should be evaluated and treated with ventricular drain placement and ICP monitoring when appropriate. For centers without this level of support, transfer is recommended to reduce mortality.[233,234]
4. Patients with ICH can have myriad issues that span multiple clinical domains and can trigger rapid clinical change, supporting the use of a multidisciplinary team care.[231,235,236] The highest-risk period for neurological decline is within the first 12 hours after the hemorrhage, with deterioration events becoming uncommon after 48 hours.[245,246] The ability to affect the patient's clinical course often rests on the ability to detect changes in the neurological examination accurately and consistently. Patients with ICH can benefit from neuromonitoring by staff trained in neurological assessment. When detected in a timely manner, these neurological changes can lead to changes in management.[99,102]
5. Patients may require invasive mechanical ventilation to ensure adequate airway protection and adequate gas exchange. It is reasonable to consider patients with decreased level of consciousness (eg, GCS score ≤8) or a declining neurological examination for invasive mechanical ventilation. Even in cases when the patient can demonstrate adequate gas exchange, neurological injury may limit the patient's ability to protect their airway, heralding a need for invasive support. Not all centers are capable of caring for complex or unstable patients. Stabilization of the patient's hemodynamic profile and airway takes priority before transfer unless the facility lacks this capability, in which case transfer to a higher level of care should not be delayed. There are no randomized data to support these recommendations on the transfer of patients with ICH. These concepts are not disease specific, but they are reasonable and likely represent the safest approach when considering a patient with ICH for transfer.
6. Determination of the appropriate level of monitoring for patients with ICH can be challenging.[247] Patients with mild to moderate ICH may, under certain conditions, be monitored safely in a dedicated stroke unit or step-down unit. A prospective observational study of 10 811 consecutive patients with spontaneous ICH who were not comatose and did not require mechanical ventilation in the first 24 hours from admission found that treatment in a stroke unit was associated with improved functional outcomes compared with treatment in either an ICU (OR, 1.27 [95% CI, 1.09–1.46]) or a general ward and that mortality was higher in an ICU (OR, 2.11 [95% CI, 1.75–2.55]) or a general ward compared with a stroke unit.[237] In a subgroup analysis of severely affected patients (NIHSS score 10–25), adjusted mortality was not different when stroke units were compared with neurointensive care units, although the odds of a poor outcome (mRS score >3) was significantly lower for patients treated in a neurointensive care unit (OR, 0.45 [95% CI, 0.26–0.79]). Other nonrandomized prospective studies that included patients with ICH have reported reduced fatality and improved outcomes, especially at longer-term follow-up.[238,248] A

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prospective study of 105 043 stroke admissions from the Swedish Stroke Register (2001–2005) reported decreased mortality and institutional living after 3 months for patients admitted to stroke units compared with other types of wards and a relative benefit for patients with ICH (hazard ratio [HR], 0.61 [95% CI, 0.58–0.65]).[238] A systematic review and meta-analysis of 8 older RCTs (1993–2004) comparing stroke unit care with general ward care found that patients with ICH benefit at least as much as patients with ischemic stroke from stroke unit care in terms of reduced death and dependency.[231] Other retrospective studies have identified criteria that predict low to no occurrence of readmission to an ICU after initial admission to a stroke unit or step-down unit.[249–251] Criteria include low ICH volume (<20 mL), low NIHSS score (≤10), high GCS score (≥13), minimal or no IVH, and absence of uncontrolled BP and respiratory failure.

7. ICH is a complex clinical event that has been shown to benefit from specially trained, multidisciplinary care. Patients with moderate to severe ICH (suggested by volume ≥30 mL), IVH, clinical hydrocephalus, or infratentorial location carry an increased risk of clinical decline. These patients have been shown to benefit from a neuro-specific ICU compared with a general critical care unit in terms of reduced mortality, length of stay (LOS), and duration of mechanical ventilation and improved outcomes.[235,236,239–241,252,253] The postulated reasons for the improvement in outcomes are varied and range from improved quality metrics to enhanced ability to detect neurological changes with specially trained nursing staff.[235,240] In 1 study, having a full-time intensivist was associated with a lower mortality rate.[239]
8. Neurosurgical intervention can alter the clinical course for a subset of patients with ICH. Several studies sought to provide guidance for which patients are best suited for neurosurgical clinical support. Patients with IVH or infratentorial location may benefit from availability of neurosurgical care.[102,233,234,254] The difficulty in interpreting these data is that the neurosurgical contribution to care is rarely isolated. One study included neurosurgical consultation in a care bundle with BP control and anticoagulation reversal and found a significant benefit on mortality.[233]
9. There are several potential indications for neurosurgical evaluation in patients with supratentorial ICH. In an effort to assist clinical decision-making, several studies attempted to highlight clinical factors that conferred a need for neurosurgical evaluation.[102,233,234,255] Patients with moderate to severe supratentorial ICH (identified in most studies by volume ≥30 mL or GCS score <8) may benefit from neurosurgical evaluation.[233,234,254]

### *Knowledge Gaps and Future Research*

- More prospective studies are needed to confirm which patients are best cared for in neuro-specific ICUs, stroke units, or step-down units.
- Most studies of patients with ICH excluded those with limitations on neurocritical care interventions according to the patient's goals of care. Limitations in life-sustaining treatments do not necessarily indicate comfort care only (Section 7.2, Decisions to Limit Life-Sustaining Treatment). There is opportunity to define the scope, efficacy, and outcomes for patients who have a priori directives for limited interventions in the context of ICH.
- There are no data on ICH-specific recommendations for the optimal timing and care bundles for transfer to facilities with appropriate resources such as defining which patients with ICH need to be intubated before transfer.
- From existing data, it has been difficult to ascertain the individual impact of specialized nursing care, neuro/critical care, neurosurgical care, BP control, and reversal of coagulopathy. From a practical perspective, these care clinicians and interventions are bundled in such a way that, for most high-volume treatment centers, it may not matter. However, for smaller centers that see a smaller number of patients with ICH, being able to provide optimal care for a subset of patients with ICH who do not need the entire bundle might be of value.
- Caring for severely affected patients with ICH is challenging. There is limited understanding of and methodology for mitigating the distress of caring for patients with ICH on hospital staff.

### *5.3.2. Prevention and Management of Acute Medical Complications*

**Recommendations for Prevention and Management of Acute Medical Complications**
**Referenced studies that support recommendations are summarized in Data Supplements 30 through 34.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. In patients with spontaneous ICH, the use of standardized protocols and/or order sets is recommended to reduce disability and mortality.[256–259] |
| 1 | B-NR | 2. In patients with spontaneous ICH, a formal dysphagia screening protocol should be implemented before initiation of oral intake to reduce disability and the risk of pneumonia.[256,260–265] |
| 2a | C-LD | 3. In patients with spontaneous ICH, continuous cardiac monitoring for the first 24 to 72 hours of admission is reasonable to monitor for cardiac arrhythmias and new cardiac ischemia.[266–268] |
| 2a | C-LD | 4. In patients with spontaneous ICH, diagnostic laboratory and radiographic testing for infection on admission and throughout the hospital course is reasonable to improve outcomes.[269–273] |

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### Synopsis

In the first hours and days after ICH, the focus and management goals of physicians and nurses are directed not only at treating the ICH and preventing HE but also at early identification and prevention of acute medical complications. Problems related to impaired swallowing, immobility, hemodynamic response and stability, infection, intensive care delirium, and altered consciousness are among the issues that neuroscience physicians and nurses must address throughout the patient's hospital course. Medical complications can range in severity but are associated with increased LOS, increased rates of mortality, and worse functional outcomes at 90 days.

### Recommendation-Specific Supportive Text

1. The use of standardized order sets and protocols for prevention of complications is well established in the literature for all types of patient-specific care. The QASC trial (Quality in Acute Stroke Care) evaluated nurse-driven protocol implementation in 19 Australian acute stroke units from 2005 to 2010.[258] This large trial showed evidence that early implementation of treatment protocols (within 72 hours of admission)—monitoring fever, hyperglycemia, and swallowing dysfunction in acute stroke units—was shown to decrease LOS, death, and disability of patients at 90 days,[256] with sustained benefits on long-term survival at 4 years (>20%) compared with the control units.[258] The use of integrated care pathways or multidisciplinary communication tools such as order sets or protocols improves timely assessments, clinical documentation, and communication and decreases LOS.[257] Hospitals with higher use of standardized order sets and adherence to specific pathways are associated with overall decreased complication rates related to infection, pneumonia, and hyperglycemia for patients with stroke.[259]
2. The risk of death resulting from pneumonia for patients with stroke is ≈35%.[262] The use of a validated swallow assessment tool and standardized dysphagia screening protocols in conjunction with treatment protocols to manage fever and hyperglycemia was associated with reduced death and disability at 90 days in a single-blind cluster RCT.[256] The ASSIST (Acute Screening of Swallow in Stroke/TIA) dysphagia screening tool was administered by a trained nurse or a speech pathologist. In a prospective open-label nonrandomized study, guideline-based protocols compared with conventional care also were associated with lower risk of pneumonia, mechanical ventilation, and 90-day mortality.[264] Patients with a positive dysphagia screen have a significantly higher 5-year mortality rate,[261] and for this reason, early identification is key for not only good long-term outcomes but also survival. Comparison of rates of pneumonia between sites with formal swallow screening protocols and sites with no formalized screening found a significant difference of 2.4% (formal screen) versus 5.4% (no formal screen).[262] Implementation of a targeted nursing bedside swallow evaluation intervention has been shown to cut rates of pneumonia in half (6.5%–2.8%) at some sites[265] and thus supports the need for nurse education in swallow assessment interventions. Two systematic reviews support decreased rates of stroke-associated pneumonia and inpatient deaths with early dysphagia screening, specialist-driven swallow assessment, and formal written protocols that are implemented before any oral intake.[260,263] All studies support early evaluation with a formal dysphagia screening tool.
3. There is evidence to suggest that patients with stroke may have up to a 30% risk of developing significant cardiac arrhythmias[266] during their hospital admission. Evaluation with continuous cardiac monitoring for the first 24 to 72 hours of admission, the time frame in which many of these arrhythmias are seen, is reasonable, depending on the clinical severity of the ICH. Individuals of older age with a larger lesion (>5 cm) had a statistically significant higher likelihood of developing clinically relevant arrhythmias that may require acute intervention.[266] Another study found that ≈25% of patients with stroke experienced cardiac arrhythmias and that most of these were in the first 72 hours of admission.[267] Neither of these studies were predictive of long-term outcomes or mortality but rather provided information on monitoring and treatment implications for the patient. Common admitting interventions to consider are 12-lead ECG, troponin level, and placing the patient on continues cardiac monitoring on arrival.
4. Infectious complications are associated with poor long-term outcomes, including readmission within the first 30 days after ICH.[272,273] A study found that patients with IVH ($P<0.001$) and patients with ICH scores >2 also had higher risk of infectious complications ($P=0.0014$).[271] ICH score >2 was found to be a significant risk factor for infectious complications (OR, 1.7 [95% CI, 1.2–2.3]; $P=0.02$).[269] These studies used these findings to guide risk assessment and diagnostic testing, which included chest radiographs; urinalysis; white blood cell counts; serum C-reactive protein; blood, urine, or sputum cultures; and, if indicated, cerebrospinal fluid. It is reasonable for all patients with ICH, especially those with larger hematomas, including IVH, to be monitored closely for fevers and signs of infection throughout the course of their hospital stay to reduce LOS, decrease mortality, and improve long-term functional outcomes. None of the studies provide prescriptive guidance on frequency of specific diagnostic tests or treatment of infectious processes.

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### Knowledge Gaps and Future Research

- Additional diagnostic tests for early identification of infectious processes are not routinely necessary for multiple reasons (eg, cost and patient comfort). There is some evidence to support that early markers such as albumin levels may be early predictors of patients at high risk of infection, but none is yet validated for clinical use.
- There is a lack of data on prevention of infectious complications and interventions to reduce hospital-acquired pneumonia, especially in nonventilated patients with ICH.
- More studies guiding additional follow-up and therapies in the postacute phase for patients with both ICH and cardiovascular disease would potentially provide benefit because their all-cause long-term mortality may be increased.
- Growing evidence suggests that inpatient delirium can affect patients' LOS and long-term functional outcome, although there are no tools specific to ICH-related delirium and no standards or specific interventions to affect this patient population. Until such ICH-specific delirium studies are performed, clinicians will commonly apply guidance that has been developed for ischemic stroke.[274]

### 5.3.3. Thromboprophylaxis and Treatment of Thrombosis

**Recommendations for Thromboprophylaxis and Treatment of Thrombosis Referenced studies that support recommendations are summarized in Data Supplements 35 through 40.**

| COR | LOE | Recommendations |
|---|---|---|
| Prophylaxis | | |
| 1 | B-R | 1. In nonambulatory patients with spontaneous ICH, intermittent pneumatic compression (IPC) starting on the day of diagnosis is recommended for VTE (DVT and pulmonary embolism [PE]) prophylaxis.[275,276] |
| 2a | C-LD | 2. In nonambulatory patients with spontaneous ICH, low-dose UFH or LMWH can be useful to reduce the risk for PE.[277–280] |
| 2b | C-LD | 3. In nonambulatory patients with spontaneous ICH, initiating low-dose UFH or LMWH prophylaxis at 24 to 48 hours from ICH onset may be reasonable to optimize the benefits of preventing thrombosis relative to the risk of HE.[277,281,282] |
| 3: No Benefit | B-R | 4. In nonambulatory patients with spontaneous ICH, graduated compression stockings of knee-high or thigh-high length alone are not beneficial for VTE prophylaxis.[276,278,283,284] |
| Treatment | | |
| 2a | C-LD | 5. For patients with acute spontaneous ICH and proximal DVT who are not yet candidates for anticoagulation, the temporary use of a retrievable filter is reasonable as a bridge until anticoagulation can be initiated.[285] |
| 2b | C-LD | 6. For patients with acute spontaneous ICH and proximal DVT or PE, delaying treatment with UFH or LMWH for 1 to 2 weeks after the onset of ICH might be considered.[286,287] |

### Synopsis

Mechanical DVT prophylaxis is rarely contraindicated, and the writing group recommends using IPC devices from the day of diagnosis of ICH on the basis of a large RCT[283] and network meta-analysis of 4 RCTs.[276] A meta-analysis of 4 studies demonstrated that heparin or LMWH reduces the risk of PE[278] when initiated 48 to 96 hours after onset of the hemorrhage or the diagnosis without a significant increase in hematoma enlargement.[277,279,281,282] Graduated compression stockings of any length are not effective against symptomatic DVT according to 2 large RCTs and 2 meta-analyses.[276,278,283,284] The balance between avoidance of recurrent ICH and appropriate treatment of the VTE to evade potentially fatal PE is challenging, especially during the first few days after onset of ICH. In a large registry of patients with VTE, insertion of an inferior vena cava (IVC) filter for those at a high risk of bleeding reduced the risk for PE-related death and for recurrent VTE compared with no IVC filter.[285] In 2 retrospective studies on patients with trauma-associated ICH and symptomatic VTE, initiation of therapeutic anticoagulation 1 to 2 weeks after the onset of ICH appeared safe with regard to HE.[286,287]

### Recommendation-Specific Supportive Text

1. The in-hospital incidence of thromboembolic complications in patients with ICH is ≈7%,[288] and the risk of DVT is 4 times higher than in patients with acute ischemic stroke,[289] attributable in part to the fear of worsening hemorrhage and initial contraindication to pharmacological prophylaxis. A network meta-analysis showed that IPC devices were more effective than compression stockings to reduce VTE in patients with acute ICH.[276] The CLOTS Trial (Clots in Legs or Stockings After Stroke) 3 was the largest of the RCTs, even when considering the subset of the study population who had hemorrhagic stroke (13%).[275] In the entire study population, there was a reduction of symptomatic and asymptomatic proximal DVT compared with control, although the reduction was statistically significant only for asymptomatic DVT. There was a trend toward reduced mortality in the IPC group. In this study, it was also observed that patients in the IPC group had increased risk of skin breaks.[275]
2. In a meta-analysis of 2 RCTs and 2 observational studies with a total of 1000 patients with ICH, prophylaxis with any type of heparin versus compression stockings (3 studies) or control (1 study) resulted in a significant reduction of the risk of PE with a nonsignificant increase in the risk of HE and no significant difference in DVT or death.[278] The heparin regimens and the time of initiation of pharmacological prophylaxis (24–96 hours from admission) differed between the studies. The duration of follow-up was only 10 days in 1 study[277] and was

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not reported in another study.[280] In a more recent meta-analysis of 9 studies and >4000 patients but addressing only safety outcomes, prophylaxis with any type of heparin was not associated with a significant increase of HE or extracranial hemorrhage, an increase in mRS scores of 3 to 5, or an increase in numbers of Glasgow Outcome Scale scores of 2 to 3.[279] Only 1 of the 9 studies had a low probability of bias.

3. There is clear indication for beginning VTE prophylaxis after ICH, with the goal of selecting the optimal post-ICH timing that maximizes benefits of VTE prophylaxis while minimizing risk of promoting ICH expansion. One small RCT[277] and 2 larger retrospective studies[281,282] addressed the timing of first dose of UFH or LMWH prophylaxis after ICH in terms of safety. The incidence of rebleeding or HE was not higher in the early start versus the delayed start group in any of the studies. An important point is that, in the retrospective studies, those with larger hematomas tended to be selected for later start times. The early start was 4 days (versus 10 days) after the ICH diagnosis in the RCT,[277] a median of 42 hours after admission in the larger retrospective study (comparing initiation of VTE prophylaxis within 48 hours of admission versus >48 hours),[281] and within 48 hours from symptom onset in the smaller retrospective study.[282] The earliest start for any patient in these studies was 25 hours after admission. In a multivariable analysis, the hematoma size, but not timing of prophylaxis, was independently associated with HE.[282] It may be reasonable to first document hemorrhage stability on CT if LMWH prophylaxis is started in the 24- to 48-hour window after ICH onset. In another large observational study with start of prophylaxis (UFH or LMWH) 0 to 1 days after CT demonstrating stability, intracranial hemorrhagic complications were observed in 1.7%.[290]
4. A meta-analysis of 2 RCTs and 2 observational studies showed that graduated compression stockings, which were used in 3 of the comparator groups, were less effective than pharmacological prophylaxis to reduce PE.[278] In a large RCT (CLOTS Trial 1), thigh-length compression stockings were not more effective than control to reduce the risk of DVT in patients with stroke, although only 9% of those had ICH.[283] In a second large RCT, again with only 12% of cases having hemorrhagic stroke, thigh-length stockings were more effective than knee-length stockings in lowering the incidence of DVT, but the reduction was significant only for asymptomatic proximal DVT.[284] Compression stockings were less effective than IPC to reduce VTE in a network meta-analysis of 3 studies and a subset from the CLOTS Trial 3, focusing on patients with ICH.[276] The design of all the studies included screening with compression ultrasound for DVT, thereby also including asymptomatic events in the efficacy outcome.
5. In the RIETE registry (Computerized Registry of Patients With Venous Thromboembolism) of >40 000 patients with VTE, a subset of 344 cases with IVC filter insertion attributable to high risk of bleeding were matched with an equal number of patients without IVC filter with the use of propensity scores.[285] The 30-day all-cause mortality did not differ between the groups, but those with IVC filter had a lower risk for PE-related death and higher risk for recurrence of VTE. The number of patients with high bleeding risk attributable to recent ICH is not provided.
6. With regard to treatment of VTE, in a retrospective cohort study of 2902 patients with spontaneous ICH, VTE was diagnosed in 3% of the cases, but this complication was independently associated with an mRS score ≥4 at discharge and at follow-up after 3 months.[291] In a small retrospective study of patients with traumatic ICH, UFH or LMWH was initiated for treatment of VTE when the neurosurgeon felt this was safe, on average 13 days after admission, and only 1 patient experienced minimal expansion of the ICH.[286] In a second, slightly larger retrospective study of traumatic ICH and VTE, those with progression of the hematoma had anticoagulant therapy initiated after a median of 5.5 days from the injury, whereas those without expansion had their anticoagulation started after a median of 10 days.[287] In this study, only 40% of the hemorrhages were intraparenchymal. Factors that should go into the consideration of the timing of anticoagulation are size of the hematoma, patient age, and extent of the VTE.

### *Knowledge Gaps and Future Research*

- It is unknown whether graduated compression stockings or IPC devices increase the efficacy of VTE thromboprophylaxis when added to pharmacological prophylaxis or allow greater delay in initiating pharmacological prophylaxis in patients with acute ICH.
- It is uncertain whether IPC devices reduce the risk of symptomatic DVT or improve functional outcomes in patients with acute ICH.
- There is currently insufficient evidence to determine the safety of LMWH prophylaxis during the first 48 hours after ICH onset. A question that should be tested is whether demonstration of stability of the hematoma by repeat imaging is useful for deciding on the safety of initiation of pharmacological prophylaxis 24 to 48 hours after onset of symptoms.

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- A large prospective study comparing 2 time points for initiation of pharmacological prophylaxis in patients with ICH should be performed.
- Prophylactic insertion of IVC filters was shown to lack benefit in a large RCT in trauma patients, but data are lacking for patients with spontaneous ICH.
- The effectiveness of IVC filters specifically in patients with ICH and early onset of VTE has not been studied.
- The earliest time point for anticoagulant treatment of VTE in patients with spontaneous ICH is not well established because the studies were in trauma-associated ICH. Timing of initiation of anticoagulation for VTE in the presence of an EVD and after surgical decompression also has limited data and high practice variability.
- Future studies should address whether anticoagulation for VTE in spontaneous ICH should be started with full therapeutic dose or with gradual increases of the dose.
- Future studies should address whether anticoagulation for VTE in spontaneous ICH should be started with UFH, LMWH, or DOACs.

### 5.3.4. Nursing Care

**Recommendations for Nursing Care**
**Referenced studies that support recommendations are summarized in Data Supplements 41 and 42.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-LD | 1. In patients with spontaneous ICH, frequent neurological assessments (including GCS) should be performed by ED nurses in the early hyperacute phase of care to assess change in status, neurological examination, or level of consciousness.[61,292–294] |
| 2a | C-LD | 2. In patients with spontaneous ICH, frequent neurological assessments in the ICU and stroke unit are reasonable for up to 72 hours of admission to detect early ND.[99,245,292,294] |
| 2a | C-LD | 3. In patients with spontaneous ICH, specialized nurse stroke competencies can be effective in improving outcome and mortality.[295–297] |

#### Synopsis

Nursing care for the patient with ICH is complex and multifaceted, often requiring critical management of hemodynamics such as BP, fever control, airway management, diagnostic laboratory and radiographic testing, assessment and management of ICP, frequent neurological assessments, and prevention of secondary complications. Nurses must have the education and knowledge to recognize stroke symptoms and the training to activate protocols for prompt assessment and management by the stroke team. Understanding the importance of the "why" (to identify ND early) and "how" (GCS or NIHSS) of neurological assessments will aid nurses in providing focused, quality assessments in a timely manner. Five studies highlight the significant negative impact that early and delayed ND have on patient mortality and functional outcome. As many as 22.6% of patients with ICH had ND in the ED,[61] whereas as many as 70% had ND in the first 24 hours of admission.[292] Specialized nurse competency training programs are associated with increased nursing satisfaction and have been shown to improve compliance with stroke evidence-based protocols.[296]

#### Recommendation-Specific Supportive Text

1. Frequent occurrence of early ND in patients with ICH is well established in multiple studies, and for this reason, ED nursing neurological assessments must be reliable and frequent. There are multiple assessment tools from which to choose, but one of the easiest and most universal is the GCS. The GCS allows straightforward evaluation of mentation and recognition of decline in patients with ICH. Proper training is required to assess this scale. One study identified patients with ICH in the prehospital to early postarrival stage as more likely to have ultraearly neurological decline compared with patients with ischemic stroke (30.8% versus 6.1%).[293] These patients with ultraearly neurological decline and early ND have increased mortality and poor functional outcomes at 90 days. Timely interventions from nurses and physicians are driven by early identification of ND by the nurse through robust, reliable, and frequent GCS examinations. The frequency of neurological assessments depends on both physical location and clinical condition of the patient. The study that identified ultraearly neurological decline performed 3 serial GCS evaluations in the ultraearly time period (first 2.5 hours since onset), during initial prehospital assessment, at initial ED arrival, and early in the ED course.
2. Frequent neurological and vital sign assessments of patients with ICH are indicated to capture ND and prevent secondary complications. One study found that nursing examination discovered up to 54% of ND leading to intervention (ie, surgery or placement of ventriculostomy) versus 46% of ND identified by neuroimaging changes.[102] These data highlight the opportunity and impact that nursing examinations have on patient care and potential outcomes. Studies indicate that patients are at highest risk of ND in the first 12 to 24 hours of ICH onset and up to 72 hours after admission.[102,292] In a prospective observational study of hourly neurological checks in a neurocritical care unit, change in GCS score within the initial 12 hours was a significant predictor of worse functional outcome at 90 days.[245] In the ICU, especially for patients with ICH of higher clinical severity, neurological assessments are typically performed hourly for the first 24 hours or until the ICH is stable. However, around-the-clock nursing interventions run the risk

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of ICU delirium and sleep deprivation, which may have further negative impact on patient functional outcome, cognition, and quality of life.[246,298] Staff training and care plans should be individualized to illness acuity with consideration of the need for frequent neurological assessments in the acute phase.

3. Nurse stroke competencies are a hallmark of providing evidence-based care. Growing literature supports the need for standardizing formal training for nurses caring for patients with ICH. To date, few studies have compared outcomes or quality of care between nurses with formal competency training and those without such training. One study found lower death rates among patients with stroke admitted to teaching hospitals, with an increased number of doctor and nursing specialists and increased nursing resources.[295] Although the study suggests that nurses at teaching hospitals with more available staff may affect mortality outcomes, it does not clearly define nurse-driven stroke care competencies. Another study highlights increased nursing stroke care knowledge and increased compliance to stroke care guidelines with the introduction of a formal stroke competency program.[296] During the analysis of this intervention, it was found that nurses who held specialized certifications scored better in adherence to protocols and knowledge assessment. These data highlight the opportunity for organizations, hospitals, and stroke teams to consider the development of a stroke competency training program and to foster and encourage more nurses to apply for specialized certification.

### Knowledge Gaps and Future Research

- The benefit versus risk of frequent nursing neurological and vital sign assessments is not well established in the literature, leaving a wide range of recommendations. Opportunities exist for clearer delineation of the time frame in which patients should be receiving hourly nursing assessments and criteria that help to establish when frequent monitoring is no longer of value and may affect recovery.
- The effects of nursing intervention on cerebral hemodynamics are poorly understood. Nursing care is multifaceted and wide-ranging, depending on the needs of the patient, and can include position changes, oral care, neurological and physical examinations, and wound care. Research evaluating the impact of clustered nursing care in the ED, ICU, and stroke unit on patient outcomes is needed.
- Many studies provide evidence that ND, early or delayed, is prevalent in the ICH patient population. No studies have addressed how nursing actions may help to prevent ND. This is poorly understood and leaves a gap in guiding nursing care in what type of preventive measures may reduce ND in the acute phase of ICH.
- Caring for severely affected patients with ICH is challenging. The potential distress of perceived inappropriate care in nurses is an important topic for future research.

## 5.3.5. Glucose Management

**Recommendations for Glucose Management**
**Referenced studies that support recommendations are summarized in Data Supplements 43 and 44.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-LD | 1. In patients with spontaneous ICH, monitoring serum glucose is recommended to reduce the risk of hyperglycemia and hypoglycemia.[256,299] |
| 1 | C-LD | 2. In patients with spontaneous ICH, treating hypoglycemia (<40–60 mg/d, <2.2–3.3 mmol/L) is recommended to reduce mortality.[299–301] |
| 2a | C-LD | 3. In patients with spontaneous ICH, treating moderate to severe hyperglycemia (>180–200 mg/dL, >10.0–11.1 mmol/L) is reasonable to improve outcomes.[78,302–307] |

### Synopsis

Glucose monitoring and management are often considered part of the general care of all patients, including those with ICH. One randomized controlled study of mixed stroke subtypes showed that a bundled care approach, including glycemic control, temperature management, and dysphagia screening, improved outcomes.[256] Hyperglycemia on presentation may herald a worse prognosis.[308,309] However, tight glucose control may increase the risk of hypoglycemic events and worsen outcomes.[299–301] The ideal evidence-based approach to glucose management in patients with ICH has remained elusive.[310]

### Recommendation-Specific Supportive Text

1. Monitoring serum glucose is important because it can provide an opportunity to intervene in the event of hyperglycemic or hypoglycemic events.[256,299] The QASC study, a single-blind cluster RCT, investigated an intervention of treatment protocols to manage fever, hyperglycemia, and swallowing dysfunction compared with no intervention and found that patients in the intervention group were significantly less likely to be dead or dependent at 90 days, although the impact of each specific intervention could not be determined.[256]
2. No trials have analyzed the effects of untreated hypoglycemia given the known acute clinical risks. The range of blood sugars outlined (<40–60 mg/dL, 2.2–3.3 mmol/L) reflects the thresholds for treatment for hypoglycemia in studies reviewed for this guideline.[299–301,309] The NICE-SUGAR trial (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation)

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randomly assigned patients in the ICU to either intensive glucose control (target, 81–109 mg/dL) or conventional glucose control (<180 mg/dL) and found that intensive glucose control resulted in increased all-cause mortality at 90 days.[299] An important finding was that severe hypoglycemic events (glucose ≤40 mg/dL) were significantly more common in the intensive control group compared with the conventional control group (6.8% versus 0.5%). It was unclear whether lower blood glucose levels, higher administration of insulin, or other factors accounted for this finding. However, in a prospective observational study of patients with severe brain injury, tight systemic glycemic control (80–110 mg/dL) was associated with low cerebral microdialysis glucose and brain energy crisis, which were correlated with increased hospital mortality.[300] Balancing the risks of hypoglycemia and hyperglycemia, both of which may worsen outcomes in patients with ICH, may justify treating low blood glucose at higher thresholds than studied in general critical care populations. The risk of treating hypoglycemia is exceedingly low, and treatment is highly recommended despite a low quality of evidence.

3. No trials have evaluated untreated hyperglycemia, rendering the data for this approach limited. Hyperglycemia appears to be an independent predictor of poor outcomes. However, the relationship among serum glucose, the timing of that measurement, and the presence/absence of comorbid diabetes remains unclear.[78,302–307] The optimal glucose level at which treatment should be initiated and the target range are not clear because the upper limit of tolerable hyperglycemia varies between studies. If carefully approached, the risk of treating moderate to severe hyperglycemia should be relatively low and outweighed by the potential benefit. However, in the NICE-SUGAR trial, in patients receiving general critical care, a blood glucose target of <180 mg/dL was associated with lower mortality than a target of 81 to 108 mg/dL, suggesting that targets for treating hyperglycemia should be less intensive in critically ill adult patients.[299] In most studies, hyperglycemia is managed by either a subcutaneous insulin or an intravenous insulin infusion protocol.

### Knowledge Gaps and Future Research

- Optimized serum glucose targets and the optimal agents for glucose control in patients with ICH have not been defined.
- The relationship among serum glucose, diabetes, and functional outcomes in patients with ICH remains unclear.
- There is a paucity of data on the impact of postprandial glycemic response in patients with ICH and the effect on outcomes.

## 5.3.6. Temperature Management

**Recommendations for Temperature Management**
**Referenced studies that support recommendations are summarized in Data Supplements 45 and 46.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | C-LD | 1. In patients with spontaneous ICH, pharmacologically treating an elevated temperature may be reasonable to improve functional outcomes.[311–313] |
| 2b | C-LD | 2. In patients with spontaneous ICH, the usefulness of therapeutic hypothermia (<35°C/95°F) to decrease peri-ICH edema is unclear.[314–317] |

### Synopsis

Temperature abnormalities in the setting of acute ICH are common and can occur in >30% of patients with ICH at some point during their hospitalization.[318–321] Fever appears to be associated with both higher clinical severity and worse outcomes[322]; however, evidence for whether treating fever improves outcomes is conflicting.[311,313] The challenge in interpreting this body of literature includes variable but often small sample sizes, few RCTs, different definitions of fever, and different therapeutic approaches addressing fever. Although many empirically treat fever, some data suggest a judicious approach. One study noted that 90% of patients with ICH met systemic inflammatory response syndrome criteria within the first 24 hours of admission. As part of their evaluation, blood cultures were obtained that provided a diagnostic yield of 0.1%, leading to increased costs of care.[323]

### Recommendation-Specific Supportive Text

1. Fever in patients with ICH has been associated with worse outcomes.[318,321] Treating fever seems reasonable; however, there is less evidence that therapeutic temperature modulation improves outcomes.[315,316,320] One pilot study of therapeutic temperature modulation with a surface device for fever with a normothermia target observed no improvement in outcomes but reported increased duration of sedation, days of mechanical ventilation, and ICU LOS.[320] Because of the variability in definitions of fever used in the literature (ranging from 37.7°C/99.5°F to 38.3°C/100.9°F), this guideline uses the term elevated temperature. In addition, there is significant variability in the literature on the approach to addressing fever, for example, pharmacotherapy versus catheter-based thermal management.[312] A multicenter RCT in patients with stroke (ischemic plus hemorrhagic) randomly assigned treatment with paracetamol for body temperature 36°C to 39°C within 12

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hours of symptom onset and reported no improvement in expected functional outcome except in a post hoc analysis of patients with baseline temperature of 37 °C to 39 °C.[313] In a prospective database, pharmacological treatment of temperatures ≥37.5 °C for 48 hours was associated with an increased likelihood of a good outcome at 3 months.[311] Another RCT comparing catheter-based normothermia with a target temperature of 36.5 °C against conventional step-wise fever management with anti-inflammatory drugs and surface cooling reported a significant reduction in fever burden for catheter-based normothermia but no significant differences in mortality or long-term outcomes.[312] Therefore, clinical trial evidence does not support a benefit of therapeutic temperature modulation, either surface devices or catheter-based normothermia, although pharmacological treatment of fever may be associated with improved outcomes.

2. Therapeutic hypothermia (35 °C/95 °F to 36.5 °C/97.7 °F) may be a physiologically reasonable approach to reducing perihematoma edema but has not been demonstrated to be clinically beneficial. Interpretation of the data is limited by small pilot cohorts, historical control subjects, and nongeneralizable samples such as only those with large-volume hemorrhages. Most of the available data were evaluated primarily with descriptive statistics. In 2 small pilot studies, therapeutic hypothermia was associated with high survival rates and maintenance of stable perihematomal edema volume.[314–316] However, therapeutic hypothermia is not without risk and should be considered of unclear benefit.[315–317,324]

### Knowledge Gaps and Future Research

- Treating fever in patients with ICH and improving outcomes remains an opportunity for future research. It is possible that some of the early data have been limited in this regard because only recently has research started considering health-related quality of life.
- The maintenance of normothermia in patients with ICH has not been demonstrated to clearly improve outcomes and is a potential therapeutic opportunity.
- Perihematomal edema remains an important concern in patients with ICH. Whether temperature modulation improves edema or functional outcomes remains unclear.

## 5.4. Seizures and Antiseizure Drugs

**Recommendations for Seizures and Antiseizure Drugs**
**Referenced studies that support recommendations are summarized in Data Supplements 47 and 48.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-LD | 1. In patients with spontaneous ICH, impaired consciousness, and confirmed electrographic seizures, antiseizure drugs should be administered to reduce morbidity.[325,326] |
| 1 | C-EO | 2. In patients with spontaneous ICH and clinical seizures, antiseizure drugs are recommended to improve functional outcomes and prevent brain injury from prolonged recurrent seizures. |
| 2a | C-LD | 3. In patients with spontaneous ICH and unexplained abnormal or fluctuating mental status or suspicion of seizures, continuous electroencephalography (≥24 hours) is reasonable to diagnose electrographic seizures and epileptiform discharges.[327] |
| 3: No Benefit | B-NR | 4. In patients with spontaneous ICH without evidence of seizures, prophylactic antiseizure medication is not beneficial to improve functional outcomes, long-term seizure control, or mortality.[328–331] |

### Synopsis

In this guideline, the writing group uses the International League Against Epilepsy definition of seizure, "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain,"[332] and, in the context of an electrographic seizure, the definition outlined by the American Clinical Neurophysiology Society, "epileptiform discharges averaging >2.5 Hz for ≥10 s (>25 discharges in 10 s) or any pattern with definite evolution and lasting ≥10 s."[332a] New-onset seizures in the context of spontaneous ICH are relatively common (between 2.8% and 28%), and most of these seizures occur within the first 24 hours of the hemorrhage.[327,333–335] Prophylactic use of antiseizure drugs, however, is of unclear benefit. The optimal approach to monitoring patients with ICH for seizures is unclear. However, data suggest that continuous electroencephalographic monitoring for at least 24 hours is probably reasonable; patients in a coma may require more prolonged monitoring.[327] The relationship among seizures, functional outcomes, and mortality is complex and not well defined. One of the primary challenges in this area is that the studies differ on the definition of seizure and method of detection.[325,329,330] Another consideration is that seizures may be a marker of ICH rather than specifically affecting outcomes.[327]

### Recommendation-Specific Supportive Text

1. There is uncertainty about the prognostic significance of abnormal electrographic patterns in the setting of ICH.[325,326] The clinical context should

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therefore be considered in the decision-making process. The recommendation is to initiate antiepileptic medication in the context of an electrographic seizure that is clinically suspected to be contributing to the impaired consciousness in order to improve morbidity (defined as LOS >14 days or discharge to somewhere other than home or a rehabilitation facility).[325] Identifying electrographic seizures can be challenging, however, and may require consultation.

2. There are no large, prospective RCTs to demonstrate the efficacy of treating seizures in the context of ICH. One small randomized trial evaluated the use of prophylactic valproic acid and suggested no difference in mortality or long-term seizure control.[336] Other studies similarly failed to demonstrate a clear mortality benefit from treating seizures in the context of ICH.[337–339] Still others showed better outcomes in patients with post-ICH seizures.[333,334] However, given the inherent limitations in the design of the available studies and the low risk of antiseizure medications in the context of active seizures, the benefits for both abortive and preventive treatment of seizures appear likely to outweigh the risks. Risk scores such as the CAVE score[340] can be used to estimate the risk of late seizures (>7 days after ICH). However, in the absence of evidence that antiepileptic medications prevent late seizures after ICH, risk scores should not be used to guide continuation of antiepileptic drugs.
3. The primary focus is on those with possible seizures that are likely contributing to the clinical picture such as patients with ICH with impaired or fluctuating level of consciousness out of proportion to the degree of brain injury or other metabolic abnormalities. These patients may not demonstrate clear and convincing rhythmic movements consistent with typical clinical seizures. If seizures are clinically suspected in this context, it is reasonable to evaluate them with a continuous electroencephalogram for at least 24 hours. One study noted that 28% of those with electrographic seizures were detected after at least 24 hours of continuous monitoring, whereas 94% were detected with at least 48 hours of monitoring. Among patients in a coma, 36% required continuous electroencephalography monitoring for >24 hours to detect the first seizure.[327]
4. Earlier studies suggested that prophylactic antiseizure drugs such as phenytoin were associated with worse outcomes in patients with ICH.[335,341] Consequently, the use of alternative prophylactic antiseizure drugs such as levetiracetam may have become more common.[342] Recent studies have not consistently identified harm or benefit from the use of prophylactic antiseizure drugs after spontaneous ICH with respect to global functional outcomes,[328–331,343] but specific domains of abilities such as cognitive function might be negatively affected.[344] One meta-analysis (1 RCT, 7 observational studies) found that seizure prophylaxis in patients with ICH was not associated with preventing either early (<14 days from ICH) or long-term seizures.[345] Another meta-analysis reported that neither levetiracetam nor phenytoin prophylaxis was associated with worse functional outcomes at the longest follow-up or 90 days, although there was a trend toward better outcomes in populations with higher proportions of patients taking levetiracetam.[346]

### *Knowledge Gaps and Future Research*

- The relationship between seizures and outcomes and the impact of antiseizure medications, especially when given in a targeted and time-limited manner, on outcome in patients with ICH are not well defined.
- The optimal approach to the patient with ICH with impaired consciousness and an abnormal electroencephalogram is not well defined.
- There is no clear consensus on which abnormal electrographic patterns in patients with ICH and impaired consciousness, with or without seizure, have prognostic significance.

## 5.5. Neuroinvasive Monitoring, ICP, and Edema Treatment

**Recommendations for Neuroinvasive Monitoring, ICP, and Edema Treatment**
**Referenced studies that support recommendations are summarized in Data Supplements 49 through 54.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with spontaneous ICH or IVH and hydrocephalus that is contributing to decreased level of consciousness, ventricular drainage should be performed to reduce mortality.[347–350] |
| 2b | B-NR | 2. In patients with moderate to severe spontaneous ICH or IVH with a reduced level of consciousness, ICP monitoring and treatment might be considered to reduce mortality and improve outcomes.[159,351–356] |
| 2b | B-NR | 3. In patients with spontaneous ICH, the efficacy of early prophylactic hyperosmolar therapy for improving outcomes is not well established.[357–361] |
| 2b | C-LD | 4. In patients with spontaneous ICH, bolus hyperosmolar therapy may be considered for transiently reducing ICP.[362–364] |
| 3: No Benefit | B-R | 5. In patients with spontaneous ICH, corticosteroids should not be administered for treatment of elevated ICP.[365–369] |

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### Synopsis

Limited data exist with respect to the frequency of elevated ICP and its management in the setting of ICH. ICP is typically measured by insertion of ICP monitors into the brain parenchyma or an EVD into the ventricles. The current recommendations on when to use EVD, ICP monitoring, hyperosmolar therapy, and corticosteroids in patients with ICH are based primarily on data from small RCTs, retrospective series, systematic reviews, and meta-analyses. As a primary recommendation, ventricular drainage should be performed in patients with ICH/IVH with hydrocephalus contributing to decreased level of consciousness. The indications for use of ICP monitoring are less clear. In patients with ICH with a GCS score ≤8, ICP monitoring and treatment might be considered to reduce mortality and improve outcomes. Hyperosmolar therapy may be considered for transiently reducing ICP. However, early prophylactic hyperosmolar agents have not demonstrated efficacy in improving outcomes, and their efficacy remains uncertain. Corticosteroids should not be administered for the treatment of elevated ICP in the setting of ICH.

### Recommendation-Specific Supportive Text

1. Hydrocephalus (Section 5.3.1, Inpatient Care Setting, Recommendations 3, 6, and 7) is an independent predictor of mortality after ICH.[370] EVD is a lifesaving procedure that can rapidly decrease ICP secondary to hydrocephalus.[350] A retrospective review of a large series of patients with ICH with IVH demonstrates that EVD placement is an independent predictor of reduced mortality at hospital discharge in patients (GCS score >3) with hydrocephalus at presentation.[347] A multi-institutional retrospective analysis suggests that EVD use is associated with lower 30-day mortality rates in patients with greater ICH volumes, higher ICH scores, and lower admission GCS scores.[348] A systematic review demonstrates that treatment with ventricular drainage, combined with fibrinolytics, may improve outcome in patients with ICH with intraventricular extension.[349] Other studies present conflicting results. In a secondary analysis of the FAST trial (Recombinant Factor VIIa in Acute Intracerebral Haemorrhage), a small number of patients who received EVDs exhibited no overall clinical benefit.[371] In a retrospective review of primary ICH affecting the thalamus, EVD placement showed no significant correlation with clinical outcomes.[372] Small sample sizes and retrospective, post hoc analysis methods introduce significant risk of bias to these studies. Although postventriculostomy hemorrhage is reasonably common in the setting of ICH, it appears to be of minor clinical significance in the majority of patients.[373]
2. The frequency at which ICP elevations occur after ICH is unclear. A retrospective analysis of a large institutional cohort demonstrates that intracranial hypertension is common after ICH, especially in younger patients with supratentorial hemorrhage.[374] However, an analysis of 2 RCTs suggests that ICP is infrequently elevated during EVD monitoring and drainage in patients with severe IVH.[159,356] A 2019 systematic review and meta-analysis indicates that the prevalence and mortality of intracranial hypertension are high after ICH.[352] No randomized studies have addressed the utility of ICP monitoring in patients with ICH. However, multiple retrospective analyses, case series, and secondary analyses examine this topic. Studies including secondary analysis of 1 RCT suggest that increased ICP levels, durations, and variability are associated with poor outcome and mortality.[159,354–356,370] The impact of ICP monitoring on patient outcome is unclear. A retrospective database analysis suggests that ICP monitoring is beneficial in patients with ICH with moderate to severe ICH/IVH with reduced levels of consciousness, especially those with GCS scores of 9 to 12.[353] Secondary analyses of the ERICH (Ethnic/Racial Variations of Intracerebral Hemorrhage) and MISTIE III (Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation) data do not support the routine use of ICP monitoring in patients with ICH,[351,375,376] although long-term mortality in MISTIE III was significantly associated with higher proportion of time with high ICP and low CPP in monitored patients.[160] Shortcomings inherent to retrospective studies or secondary analyses such as small sample size and selection biases should be considered in the interpretation of these findings.
3. Prophylactic administration of hyperosmolar agents (including mannitol and hypertonic saline) to attain serum hyperosmolar levels has been studied in patients with ICH. Small retrospective studies suggest a potential benefit of hyperosmolar infusion on cerebral blood flow, edema evolution, and frequency of ICP crises.[376,377] The studies focused on prophylactic use of mannitol infusion have not demonstrated clinical benefit,[357,360,361] whereas prophylactic hypertonic saline infusions have not been well studied. The propensity-matched retrospective analysis from the ERICH study cohort in which 78% of treated cases received only mannitol suggested that hyperosmolar therapy is not associated with better 3-month mRS outcomes.[359] A 2007 Cochrane review concluded that there was not enough evidence to determine whether the routine use of mannitol would result in any beneficial or harmful effect.[357] A systematic review and meta-analysis conducted in 2018 determined that mannitol could lead to hematoma enlargement and did not recommend routine use in the early stage of supratentorial ICH.[360] Although the efficacy of hyperosmolar treatments to attain serum hyperosmolarity is not well established, usual supportive

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medical care includes treatment of hyponatremia and other post-ICH medical complications.

4. Hyperosmolar therapy is the principal medical strategy in the treatment of cerebral edema.[378] A 2011 meta-analysis of randomized clinical trials suggested that mannitol or hypertonic saline, in equiosmolar doses, may be effective in treating acutely elevated ICPs but that hypertonic saline is more effective than mannitol. This meta-analysis included studies of patients undergoing quantitative ICP monitoring regardless of underlying cause.[362] A retrospective analysis examined the dose of mannitol needed to reach a stable ICP level in the setting of ICH. The study found that the effect of mannitol on ICP was dose dependent during the period of ICP reduction but not after the ICP had reached a stable level.[363] The optimal mannitol dose required for individual patients with ICH with elevated ICP can be calculated by determining hemorrhage location, hematoma volume, and pretreated ICP measurement.[363] A study of 20 patients with ICH examined mean flow velocities and pulsatility indices in the middle cerebral artery territory. Results suggested that a single bolus of mannitol modifies cerebral hemodynamics (increased flow velocities in affected middle cerebral artery) in patients with ICH.[364]
5. A 1987 randomized controlled study found that dexamethasone treatment resulted in no beneficial effects and increased complications (principally infections and diabetic complications) in patients with supratentorial ICH.[368] A second RCT performed in 1989 demonstrates no differences in outcomes in patients with ICH treated with corticosteroids versus those treated without corticosteroids.[365] A 1998 RCT suggests that dexamethasone does not likely cause an unacceptably high rate of complications but also does not provide a benefit.[366] More recently, a Cochrane review[367] and a meta-analysis[369] demonstrated no clear benefit to patients with ICH treated with dexamethasone or glucocorticoids. Taken together, these studies suggest that there may be some risk, in addition to a lack of benefit, for corticosteroid administration in the setting of ICH.

### *Knowledge Gaps and Future Research*

- Because of a paucity of disease-specific data, indications for ICP monitoring in patients with ICH are often derived from the TBI literature. Guidelines suggest ICP monitoring in patients with a GCS score of 3 to 8 and maintenance of an ICP <22 mm Hg and a CPP of 50 to 70 mm Hg, depending on capacity for cerebral autoregulation. Studies focused exclusively on ICH may help to determine specific parameters that can be used to guide the monitoring and treatment of patients with ICH.
- A meta-analysis demonstrated a potential advantage of hypertonic saline over mannitol in lowering ICP across a range of neuropathologies. However, the comparative efficacies of mannitol and hypertonic saline have not been extensively studied in the setting of ICH. Future investigations could determine whether there is a greater benefit of one versus the other for patients with ICH with elevated ICP.
- Neuroinvasive monitoring is advancing rapidly. Multimodality monitoring techniques suggest that fraction of inspired oxygen, mean arterial pressure, and CPP can be used to predict changes in brain tissue oxygen. Elevated glutamate levels are noted in the perihematomal region. Small case series indicate CPP parameters and threshold pyruvate/lactate ratios that are associated with favorable outcomes after ICH. Larger future studies focused on indications and utility of microdialysis and brain tissue oxygenation measurements in the perihematomal region may help to determine optimal tissue oxygenation parameters and metabolic correlates associated with favorable outcomes after ICH.
- Hyperosmolar therapy is typically administered in 4- to 6-hour intervals. However, the duration of transient effects from hyperosmolar therapy in the setting of ICH is unclear. Further studies could determine the effective treatment durations and whether hyperosmolar agents are effective in preventing poor outcomes.

## 6. SURGICAL INTERVENTIONS

### 6.1. Hematoma Evacuation

#### *6.1.1. MIS Evacuation of ICH*

**Recommendations for MIS Evacuation of ICH**
**Referenced studies that support recommendations are summarized in Data Supplements 55 and 56.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-R | 1. For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5–12), minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic use can be useful to reduce mortality compared with medical management alone.[379–388] |
| 2b | B-R | 2. For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5–12) being considered for hematoma evacuation, it may be reasonable to select minimally invasive hematoma evacuation over conventional craniotomy to improve functional outcomes.[382,383,385–387,389,390] |
| 2b | B-R | 3. For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5–12), the effectiveness of minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic use to improve functional outcomes is uncertain.[379–385,387,388] |

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### Synopsis

MIS for supratentorial ICH has the appeal of relieving hematoma volume, reducing perihematomal edema, and, compared with conventional craniotomy, minimizing disruption of healthy brain tissue. Therefore, enthusiasm for MIS techniques to treat moderate to large ICHs during the acute phase seems intuitive. However, results from large randomized clinical trials have not been definitive.[379–388,391,392] The present guideline uses primarily data from the largest RCT of MIS (MISTIE III),[381] meta-analyses of trials comparing MIS with conventional craniotomy and standard medical care,[379,380,382–390,393–395] and smaller RCTs.[391,392,396–412] The majority of clinical trials have used ICH volume thresholds of >20 or >30 mL as an inclusion criterion. As a primary recommendation, minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration, with or without thrombolytic use, is safe and may be useful to reduce mortality. Although it may also improve functional outcomes, the LOE for this is lower. Compared with craniotomy, the mortality benefit of MIS is uncertain, although the literature supports that MIS may be considered to improve functional outcomes compared with conventional craniotomy. MIS interventions require surgeon and center skill and experience as the basis for these recommendations.

### Recommendation-Specific Supportive Text

1. Mortality, a prespecified secondary analysis in MISTIE III, was significantly lower in the MIS group compared with the standard medical care group at 7, 180, and 365 days, although the trial was neutral on the primary outcome (functional outcome benefit).[381] Although smaller, likely underpowered RCTs did not always show a mortality benefit for MIS,[392,400,401,406,408] most meta-analyses comparing stereotactic puncture or endoscopic drainage with standard medical care reported significantly decreased odds of death with any MIS compared with standard medical care.[380,382,386–390,394] Multiple safety end points were addressed in the MISTIE III trial, including symptomatic hemorrhage within 72 hours after last dose of alteplase and bacterial brain infection, which were similar between groups, indicating that stereotactic aspiration with thrombolysis appears to be safe.[381] SAEs at 30 days were significantly lower in the MIS group versus the standard medical care group. Only asymptomatic bleeding was higher in the MIS versus the standard medical care group (32% versus 8%). Other RCTs and meta-analyses confirm no significant difference in safety end points (brain rebleeding after treatment and infection) for endoscopy and stereotactic aspiration/craniopuncture techniques compared with standard medical care or craniotomy.[391,398,400,405,406,408,411–413] Most RCTs enrolled patients <80 years of age, although age did not modify the effect of surgery except in 1 meta-analysis in which improved outcomes from any surgery for ICH were found for patients 50 to 69 years of age.[393]
2. Studies comparing MIS with conventional craniotomy have shown improved outcomes with a less invasive approach, raising the possibility that open craniotomy may damage more brain tissue while removing blood. Both small RCTs[389,398,399,411,412,414] and all meta-analyses of either clinical trials alone or combined with observational studies from different settings comparing stereotactic puncture or endoscopic drainage with craniotomy have shown significantly decreased odds of functional dependence (or combined with death) and increased odds of good functional outcome with MIS.[383,385–387,389,390,394,395] A network meta-analysis suggested the highest ranking of favorable prognosis for stereotactic aspiration, followed by endoscopy, then craniotomy, and last standard medical care.[382] RCTs comparing MIS with craniotomy have included patients with ICH volume >25 mL and time interval to surgery from <6 to 72 hours after presentation. In the early surgery study, MIS showed a functional outcome benefit compared with craniotomy only if the CTA spot sign was positive but also showed a higher risk of rebleeding.[399]
3. Many small RCTs of MIS show a functional outcome benefit from MIS compared with standard medical care at follow-up times of 3 months to 1 year.[391,392,396–399,401,403,408,412,413] In the MISTIE III trial, stereotactic aspiration plus irrigation with alteplase did not improve functional outcomes at 1 year compared with standard medical care in patients with ICH volume >30 mL.[381] However, planned exploratory analyses of clot removal showed a significant association between extent of clot removal and both mortality and lower mRS score (0–3), specifically in those patients who achieved the surgical aim (end-of-treatment clot size ≤15 mL). Meta-analyses of this and smaller clinical trials and observational studies from different settings comparing stereotactic puncture or endoscopic drainage with standard medical care have shown improved functional outcomes (alone or together with survival) with MIS.[379,380,382–390,394] Most RCTs included only ICH volume >20 mL, although several included ICH volumes as low as 10 mL. One meta-analysis found that MIS was most beneficial for patients with hematoma volume between 25 and 40 mL and with a GCS score ≥9,[387] whereas MISTIE III and 2 other meta-analyses found that hematoma volume did not modify the effect of surgery.[379,381,384]

### Knowledge Gaps and Future Research

- Current evidence does not support specific recommendations for selecting candidates for surgery. A

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priori analyses focusing on clinical details, hematoma volume, patient age, GCS score (baseline clinical severity), and follow-up timing would inform future clinical trial design and recommendations.

- RCTs of MIS have not addressed a priori questions about timing of surgery and intent to stabilize ICH before surgery. Optimal time to surgical treatment with MIS remains a controversial issue primarily because of the risk of rebleeding, although reducing hematoma volume early (<12 or 24 hours) may reduce secondary brain injury and improve outcomes with no effect on bleeding risk as suggested by observational data. Several RCTs are underway that will address aspects of these questions.
- Although a functional outcome benefit of MIS compared with conventional craniotomy is reported for many RCTs, a mortality benefit is uncertain and may reflect the practice to perform craniotomy but not MIS in deteriorating patients. Most small RCTs are underpowered and did not show a mortality benefit of MIS compared with craniotomy; however, most meta-analyses of smaller clinical trials and observational studies comparing stereotactic puncture or endoscopic drainage with conventional craniotomy showed significantly decreased odds of death with MIS.
- Currently, no adequately powered clinical trial data compare different devices for MIS in ICH. Although surgeon experience and ability to achieve adequate hematoma removal with low rebleeding risk and acceptable outcomes may prove superior to a single technique, ongoing innovation with the development of new surgical devices will require comparisons of endoscopic and stereotactic techniques with thrombolysis and with potential for intrahematomal delivery of therapeutic agents. Ongoing RCTs will add useful data to these questions.

### 6.1.2. MIS Evacuation of IVH

**Recommendations for MIS Evacuation of IVH**
**Referenced studies that support recommendations are summarized in Data Supplements 57 through 62.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. For patients with spontaneous ICH, large IVH, and impaired level of consciousness, EVD is recommended in preference to medical management alone to reduce mortality.[347–349] |
| 2a | B-R | 2. For patients with a GCS score >3 and primary IVH or IVH extension from spontaneous supratentorial ICH of <30-mL volume requiring EVD, minimally invasive IVH evacuation with EVD plus thrombolytic is safe and is reasonable compared with EVD alone to reduce mortality.[415–418] |
| 2b | B-R | 3. For patients with a GCS score >3 and primary IVH or IVH extension from spontaneous supratentorial ICH of <30-mL volume requiring EVD, the effectiveness of minimally invasive IVH evacuation with EVD plus thrombolytic use to improve functional outcomes is uncertain.[382,407,415–419] |

**Recommendations for MIS Evacuation of IVH (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | B-NR | 4. For patients with severe spontaneous ICH, large IVH, and impaired level of consciousness, the efficacy of EVD for improving functional outcomes is not well established.[347–349] |
| 2b | C-LD | 5. For patients with spontaneous supratentorial ICH of <30-mL volume and IVH requiring EVD, the usefulness of minimally invasive IVH evacuation with neuroendoscopy plus EVD, with or without thrombolytic, to improve functional outcomes and reduce permanent shunt dependence is uncertain.[419,420] |

#### Synopsis

Intraventricular extension of ICH occurs in 30% to 50% of patients with ICH and predisposes to the development of hydrocephalus in approximately half of patients.[421] IVH predicts a worse prognosis secondary to increased IVH volume and blood breakdown products that promote inflammatory meningitis and hydrocephalus.[126] Insertion of an EVD to treat intracranial hypertension and remove blood products improves survival.[347–349] The addition of thrombolytic irrigation with alteplase or urokinase hastens intraventricular clot removal and results in further mortality reduction.[416,422] The current recommendations (illustrated in Figure 3) are based primarily on data from the largest RCT of intraventricular thrombolysis (IVT; CLEAR III [Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage]),[416] systematic reviews or meta-analyses of trials comparing (1) EVD with and without IVT with conservative treatment[349] and (2) IVT with either EVD plus saline or EVD alone,[415,417,418] and several smaller RCTs.[356,423–425] As a primary recommendation, EVD with IVT is safe and improves survival in patients with clinical hydrocephalus and reduced level of consciousness compared with EVD alone (or with saline irrigation). However, the benefit of EVD to improve functional outcomes is uncertain. Other interventions studied for removing large volumes of IVH and reducing permanent shunt dependence include controlled lumbar drainage combined with IVT and targeted intraventricular neuroendoscopy.

#### Recommendation-Specific Supportive Text

1. In patients with moderate to large IVH and higher clinical severity (defined in a propensity score–matched analysis as GCS score <13, ICH volume >11 mL, and Graeb score ≥7 [indicating moderate to severe IVH[348]]), EVD placement alone is associated with improved survival compared with conservative treatment.[347–349] In a large retrospective analysis with propensity score matching, EVD use was associated with higher survival in patients with severe ICH as defined above, although not overall.[348] A smaller retrospective analysis found a positive association of EVD alone with survival at hospital discharge in patients presenting with

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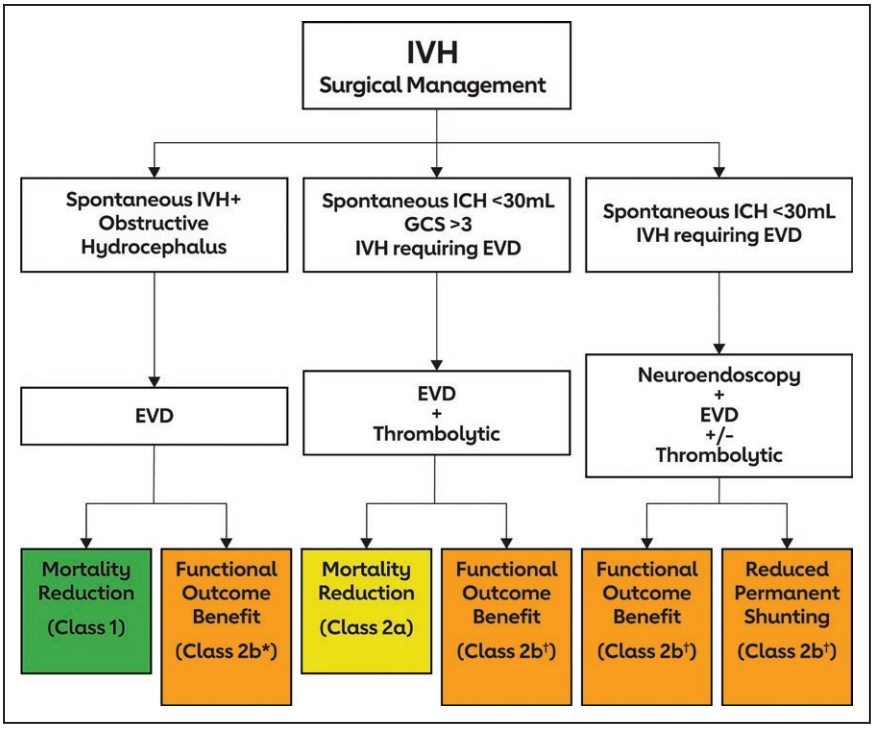


**Figure 3. Surgical management of IVH.**
EVD indicates external ventricular drain; GCS, Glasgow Coma Scale score; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage. *Not well established. †Uncertain.

hydrocephalus and a GCS score >3 after adjustment for clinical severity.[347] There were no age limits on these studies.

2. In patients with IVH obstructing the third or fourth ventricle and small- to moderate-volume ICH (<30 mL), controlled irrigation with a thrombolytic agent such as alteplase or urokinase improves survival in patients with clinical hydrocephalus requiring a routinely placed EVD. Mortality, a prespecified secondary analysis in CLEAR III, was significantly lower in the EVD plus alteplase group compared with the EVD plus saline group at 180 days.[416] Smaller RCTs also have shown a mortality benefit for IVT,[356,423–425] and all meta-analyses of RCTs with or without observational data comparing EVD alone or with saline with EVD plus alteplase or urokinase reported significantly decreased odds of death with IVT.[415,417,418] Multiple safety end points were addressed in CLEAR III, including symptomatic hemorrhage, which was not different between study groups. Both bacterial ventriculitis and SAEs were significantly less frequent in the alteplase group versus the saline-administered group, indicating that IVT appears to be safe.[416] Other RCTs and meta-analyses confirm no significant difference in safety end points (rebleeding after treatment and ventriculitis) for IVT compared with EVD alone or with saline irrigation.
3. It is not clear whether EVD plus IVT improves functional outcomes. In CLEAR III, EVD plus irrigation with alteplase did not improve functional outcomes at 180 days compared with EVD plus saline in patients with obstructive IVH and ICH volume <30 mL.[416] However, a low proportion of participants achieved near-complete clot removal, and functional benefit was reported from removing greater amounts (>85%) of IVH volume. Alternatively, the absence of benefit of IVT on functional outcome in clinical trials might also be attributable to cerebral injury associated with parenchymal hemorrhage. CLEAR III included a high proportion of patients with thalamic ICH, a location with poor prognosis. In CLEAR III, a greater proportion of patients in the IVT arm had severe disability (mRS score 5) at 180 days, suggesting that mortality reduction occurred at the expense of severe morbidity. Meta-analyses of this and smaller clinical trials and observational studies comparing IVT to EVD (with or without saline) have shown heterogeneous effects on functional outcomes from IVT, depending on time of follow-up and functional outcome scale used.[415,417,419,426] Most RCTs included patients up to 75 or 80 years of age. CLEAR III excluded patients with anticipated early withdrawal of life-sustaining therapies. For patients being considered for IVT, shared decision-making between physicians and family members is recommended to weigh mortality and functional outcome benefits with consideration of patient preferences.
4. Compared with conservative treatment, there is uncertainty over whether EVD alone improves functional outcomes. In a systematic review of studies

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including patients with nontraumatic IVH secondary to ICH or subarachnoid hemorrhage and Graeb score >7, EVD alone was not associated with return to an independent lifestyle.[349] In a large retrospective analysis with propensity score matching, EVD use was not associated with functional outcome at discharge.[348] Subgroup analysis by several clinical severity factors found that patients receiving an EVD had more disability on the mRS compared with patients who did not receive an EVD. In this retrospective cohort, it is possible that patients who received an EVD were more severely disabled at presentation, thus requiring an EVD, versus those who did not. Moreover, patients who may have died without EVD placement also may have worse outcomes. A smaller retrospective analysis found a positive association between EVD alone compared with no EVD and good outcome at hospital discharge.[347] However, retrospective studies are unable to evaluate unmeasured confounders that contribute to the decision to place EVDs in patients with IVH.

5. Endoscopic surgery for hypertensive IVH combined with EVD with or without IVT has been studied in small RCTs and observational studies.[419,420,427,428] Small RCTs have reported no significant difference in mortality rate, and 2 of them reported improved short-term functional outcomes for the endoscopic group compared with the EVD group.[427,428] One meta-analysis reported higher IVH evacuation rate, lower mortality, improved functional outcomes, and lower permanent shunt rate for endoscopic surgery plus EVD compared with EVD plus IVT.[420] No conclusive evidence was provided comparing endoscopic surgery with EVD alone. A network meta-analysis reported improved survival and functional outcomes for endoscopic surgery compared with EVD plus alteplase or urokinase, all of which were superior to EVD alone.[419] Lower rates of permanent shunting, intracranial rebleeding, or infection in the endoscopic surgery group suggest that this intervention seems safe, although no large high-quality RCTs directly comparing these interventions have been performed and risk of publication bias is high.

### Knowledge Gaps and Future Research

- Current evidence does not support specific recommendations for selecting patients with IVH for EVD in terms of timing or volume of IVH; EVD insertion rates vary widely between hospitals and regions. One retrospective analysis found that small IVH volume (Graeb score ≤2) not associated with obstructive hydrocephalus was not associated with unfavorable outcome or death after ICH, whereas a Graeb score >2 was independently associated with unfavorable outcome and higher mortality.
- Exploratory analyses of CLEAR III suggest associations of improved functional outcome in alteplase-treated patients with larger IVH volumes and randomized earlier after symptom onset. A priori analyses focusing on clinical details (IVH volume and time to initiation of thrombolytic treatment) would inform future recommendations.
- RCTs of IVT and endoscopy have not addressed a priori questions about adequate removal of IVH and optimal timing of the intervention. Further research is needed to determine functional outcome benefit of near-complete IVH evacuation compared with targeting opening of the lower ventricular system and resolution of hydrocephalus and intracranial hypertension.
- Currently, no adequately powered clinical trial data compare different surgical approaches for evacuation of IVH. Are endoscopic techniques superior to EVD plus IVT, and is addition of lumbar drainage superior to EVD alone plus IVT for outcomes or avoidance of permanent shunting?

### 6.1.3. Craniotomy for Supratentorial Hemorrhage

**Recommendations for Craniotomy for Supratentorial Hemorrhage**
**Referenced studies that support recommendations are summarized in Data Supplements 63 and 64.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | A | 1. For most patients with spontaneous supratentorial ICH of moderate or greater severity, the usefulness of craniotomy for hemorrhage evacuation to improve functional outcomes or mortality is uncertain.[380,382,384,393,429–431] |
| 2b | C-LD | 2. In patients with supratentorial ICH who are deteriorating, craniotomy for hematoma evacuation might be considered as a lifesaving measure.[382,384,429,432] |

### Synopsis

For most patients, craniotomy for spontaneous ICH remains of uncertain benefit compared with medical management alone.[429,431] RCT results have been inconclusive. Early data were mixed,[393,433–440] with 2 large RCTs finding no benefit in functional outcome or mortality.[429,431] However, the most recent of these large RCTs identified a trend toward a mortality benefit, despite a substantial medical-to-surgical crossover rate. In addition, a recent smaller single-center RCT demonstrated a mortality benefit.[432] Therefore, limited data suggest that it is reasonable to consider craniotomy as lifesaving procedure in deteriorating patients. A knowledge gap exists concerning the timing of craniotomy for ICH. A small single-arm series of 11 patients raised concern about the safety of craniotomy within <4 hours of onset,[436] and STICH (Surgical Trial in Intracerebral Haemorrhage) I and II showed increasing likelihood of achieving a good outcome within a broad therapeutic time window, although surgery was

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performed primarily >12 hours after onset.[441] Two smaller single-center RCTs requiring surgery within ≤12 hours of onset have suggested benefit.[430,437] Given these data, further research is indicated to identify whether early (<12 hours) intervention might provide benefit.

### Recommendation-Specific Supportive Text

1. Craniotomy for ICH of volume >10 mL in patients with significant neurological deficit remains of uncertain benefit compared with conservative management. Both STICH I and STICH II demonstrated no benefit in functional outcome with craniotomy in situations in which the treating neurosurgeon was uncertain about the benefits of either treatment.[429,431] A patient-level data meta-analysis performed contemporaneously suggested that certain cohorts might benefit,[393] and a smaller (n=108) single-center RCT found that craniotomy improved functional outcome.[430] Three meta-analyses published in 2020 provide mixed results: 2 meta-analyses suggest a benefit in functional outcome and mortality with any surgery,[382,384] and 1 meta-analysis found no benefit in functional outcome or mortality.[380]
2. Despite the unclear value of craniotomy to improve overall functional benefit or mortality, limited data suggest that craniotomy for hematoma evacuation might be considered as a lifesaving measure in patients who are deteriorating. STICH II found a trend toward improved mortality with surgery, despite a 21% crossover rate from medical therapy to surgery, 74% of which were attributable to deterioration.[429] Individuals who crossed over had deeper coma with worse neurological deficits than those in the early surgery group and had worse prognosis compared with individuals who did not cross over, but their surgery did not affect trial results, which were analyzed by intention to treat.[429] This suggestion of a mortality benefit was further supported by a recent small (n=61) RCT that demonstrated improved mortality with surgery[432] and 2 meta-analyses that suggest a possible mortality benefit.[382,384] Therefore, given the crossover attributable to deterioration observed in STICH II and the data suggesting a possible mortality benefit, for patients who are deteriorating, craniotomy for hematoma evacuation may be considered as a life-saving measure.

### Knowledge Gaps and Future Research

- The potential impact of timing of craniotomy for ICH on outcome remains debated. Although STICH I and II did not identify an early time effect, a significant majority of enrolled patients underwent surgery >12 hours from onset, and those with surgery <12 hours from onset were likely secondary to severe presentation or deteriorating status. A late time threshold, however, was identified in the STICH I and II cohorts, with expectations of worse outcome beyond 62 hours. Only 2 single-center RCTs have been performed that required surgery within ≤12 hours from onset. The study by Morgenstern et al,[437] although not powered for efficacy (n=34), found a promising mortality signal when surgery was performed within 12 hours. More encouragingly, Pantazis et al[430] (n=108) demonstrated a benefit in functional outcome when surgery was undertaken within <8 hours. Future multicenter research evaluating the benefit of surgery within 12 hours may clarify this knowledge gap.

## 6.1.4. Craniotomy for Posterior Fossa Hemorrhage

**Recommendations for Craniotomy for Posterior Fossa Hemorrhage**
**Referenced studies that support recommendations are summarized in Data Supplement 65.**

| COR | LOE | Recommendation |
|---|---|---|
| 1 | B-NR | 1. For patients with cerebellar ICH who are deteriorating neurologically, have brainstem compression and/or hydrocephalus from ventricular obstruction, or have cerebellar ICH volume ≥15 mL, immediate surgical removal of the hemorrhage with or without EVD is recommended in preference to medical management alone to reduce mortality.[442–444] |

### Synopsis

Spontaneous cerebellar hemorrhage is frequently associated with hydrocephalus, brainstem compression, and herniation in the confined space of the posterior fossa.[126] Therefore, hematoma evacuation is often recommended despite a lack of randomized evidence.[414] The present guideline is based primarily on data from a large individual-patient data meta-analysis with propensity score matching,[442] systematic reviews[443,444] and several retrospective studies.[254,445–451] As a primary recommendation, urgent surgical hematoma evacuation with or without EVD is recommended compared with conservative management to reduce mortality in patients with cerebellar ICH who are deteriorating neurologically, have brainstem compression and/or hydrocephalus from ventricular obstruction, or have cerebellar ICH volume ≥15 mL. The efficacy of surgical evacuation for improving functional outcomes, however, is uncertain and has not been demonstrated in retrospective studies.[442] For patients with cerebellar ICH and clinical hydrocephalus, EVD alone is, in theory, potentially harmful, especially if the basal cisterns are compressed.[452] EVD alone may be insufficient when intracranial hypertension impedes blood supply to the brainstem.[445]

### Recommendation-Specific Supportive Text

1. In an individual-patient data meta-analysis, for patients with spontaneous cerebellar hemorrhage without brainstem extension, hematoma evacuation was not significantly associated with improved functional outcomes at 3 months but was associated with survival benefit at both 3 and 12 months.[442] Mortality benefit occurred for patients with larger

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hematoma volumes (>15 mL), whereas volumes <12 mL were associated with lower likelihood of good outcome with surgery. A systematic review of 41 studies (37 retrospective and 4 prospective) reported no significant association of surgical evacuation with either mortality or functional outcomes at 6 months but, because of a large proportion of retrospective studies, suffered from a high risk of bias.[443] A large retrospective review found that pooled mortality rates were lower in patients treated with surgery compared with conservative treatment but functional outcomes were more favorable with nonsurgical management.[444] This may reflect variable indications for surgery. Another study reported mortality reduction with surgery in cases with hydrocephalus, but not without, indicating the importance of treating hydrocephalus.[450] One retrospective study reported trends for improved mortality and functional outcome for suboccipital decompression and hematoma evacuation compared with evacuation alone.[448] Most studies support a lifesaving benefit from surgery under conditions of a deteriorating clinical examination, impending brainstem compression, clinical hydrocephalus with fourth ventricle obstruction, and radiographic obliteration of basal cisterns.[442,445–448,450,451]

### *Knowledge Gaps and Future Research*

- A perceived lack of equipoise concerning the lifesaving benefits of surgical evacuation for cerebellar ICH most likely precludes the design of future randomized trials to address the question of surgical versus conservative management. The efficacy of surgical evacuation for improving functional outcomes remains uncertain.
- Previous studies have not addressed a priori questions about timing of surgery for cerebellar ICH and specifically whether initial conservative treatment compared with immediate surgical evacuation is preferable in patients with cerebellar ICH >3 cm/15 mL who are in a good clinical condition. For such patients, a retrospective study reported that an initial conservative approach often leads to good outcome and that there may be a subgroup of patients in whom surgery can be safely deferred. The optimal timing and indications of surgical treatment in large cerebellar ICH with good clinical condition are worthy of further study.
- Currently, no adequately powered studies have compared different surgical approaches for cerebellar ICH. Several small retrospective studies compared endoscopic evacuation or stereotactic aspiration with standard suboccipital craniectomy, with variable efficacy. Comparison of MIS techniques with suboccipital hematoma evacuation with or without decompression is an important topic for future clinical trials. Further investigation also is needed to determine whether MIS in patients with >15-mL cerebellar ICH volume and good clinical condition improves functional outcome compared with best medical treatment.

## 6.2. Craniectomy for ICH

**Recommendations for Craniectomy for ICH**
**Referenced studies that support recommendations are summarized in Data Supplements 66 through 68.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | C-LD | 1. In patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management, decompressive craniectomy with or without hematoma evacuation may be considered to reduce mortality.[453–460] |
| 2b | C-LD | 2. In patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management, effectiveness of decompressive craniectomy with or without hematoma evacuation to improve functional outcomes is uncertain.[458–462] |

### *Synopsis*

Large supratentorial ICH is often associated with clinical deterioration and elevated ICP that is refractory to medical management. Therefore, decompressive craniectomy is often considered as a lifesaving procedure despite a lack of strong randomized evidence. This guideline is based primarily on data from small RCTs,[458,462] retrospective series,[453–457,461,463–471] a systematic review,[459] and a meta-analysis.[460] These studies compared decompressive craniectomy with medical management or craniotomy with clot evacuation. Reports also compared decompressive craniectomy alone with decompressive craniectomy with clot evacuation. As a primary recommendation, decompressive hemicraniectomy may be considered to reduce mortality in patients with supratentorial ICH who are in a coma, have large hematomas with midline shift, or have elevated ICP refractory to medical management. No clear differences have been demonstrated between decompressive hemicraniectomy with and without clot evacuation.[461] The efficacy of decompressive craniectomy for improving functional outcomes is uncertain.

### *Recommendation-Specific Supportive Text*

1. Retrospective case series demonstrate that decompressive craniectomy is safe and feasible. The majority of studies examine patients in a coma (GCS score <8), with hematomas >30 mL, or with ICP that did not normalize with medical management.[454,458,462,463,465,466,468,471] Many include patients within 24 hours of hemorrhage. Overall, the studies suggest that surgery may improve mortality compared with medical

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management.[453–457,470] Both a meta-analysis and a systematic review suggest that decompressive craniectomy may offer mortality benefits in the setting of supratentorial ICH.[459,460] Studies included in these analyses compare decompressive craniectomy with both medical management and craniotomy with clot evacuation. The systematic review (1 RCT, 8 retrospective studies) included only patients who underwent decompressive craniectomy without clot evacuation and reported a mortality rate of 26%.[459]

2. There is less evidence of beneficial effects of decompressive craniectomy on functional outcome than on mortality. One RCT assessed decompressive craniectomy without hematoma evacuation against hematoma evacuation without decompressive craniectomy in deep supratentorial ICH.[462] This study found no difference in mortality at 6 months and slightly higher GCS score (improved outcome) for patients undergoing hematoma evacuation alone (35.3%) compared with decompressive craniectomy alone (30.7%). Another RCT assessed adding decompressive craniectomy and expansive duraplasty to hematoma evacuation versus hematoma evacuation alone for large hypertensive ICH.[458] This study demonstrated reduced mortality (10% versus 25%) and improved functional outcome (70% versus 20% with favorable outcome) at 6 months in the decompressive craniectomy plus expansive duraplasty cohort.[458] Retrospective case series that compare decompressive craniectomy and craniotomy with hematoma evacuation present conflicting results (some favor decompressive craniectomy, others favor hematoma evacuation).[463–469] A single retrospective study compared decompressive craniectomy with and without associated hematoma evacuation. Performance of hematoma evacuation did not change functional outcomes.[461] A meta-analysis (1 RCT, 7 observational studies) reported that decompressive craniectomy significantly reduced poor outcome compared with the control group, but only for studies using hematoma evacuation as control.[460] The systematic review reported a pooled favorable outcome in 53%.[459]

### *Knowledge Gaps and Future Research*

- There is a perceived lack of equipoise regarding the lifesaving benefits of decompressive craniectomy for supratentorial ICH and medical management. The efficacy of surgical evacuation for improving functional outcomes, however, remains uncertain. The currently enrolling SWITCH trial (Decompressive Hemicraniectomy in Intracerebral Hemorrhage) will investigate these questions (ClinicalTrials.gov NCT02258919).
- Previous studies have not directly addressed timing of decompressive craniectomy surgery in the setting of ICH. It is unclear whether the benefits of surgery would be greater within a specific time window. Future studies could help determine the optimal timing of decompressive craniectomy in large supratentorial ICH.
- There is also limited guidance from the literature on appropriate patient selection for decompressive craniectomy. For example, it is not known how patient-specific factors such as age, degree of language involvement, and medical comorbidities may influence mortality and functional outcomes after decompressive craniectomy for supratentorial ICH.
- The ideal decompressive craniectomy size has not been studied in patients with ICH. However, literature exists with respect to hemicraniectomy size in the setting of ischemic stroke, head trauma, and subarachnoid hemorrhage. Future studies in patients with ICH could help determine the optimal size of craniectomy flap and the effects that the size of the hemicraniectomy has on ICP measurements and patient outcome.

## 7. OUTCOME PREDICTION AND GOALS OF CARE

### 7.1. Outcome Prediction

**Recommendations for Outcome Prediction**
**Referenced studies that support recommendations are summarized in Data Supplement 69.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with spontaneous ICH, administering a baseline measure of overall hemorrhage severity is recommended as part of the initial evaluation to provide an overall measure of clinical severity.[472–474] |
| 2b | B-NR | 2. In patients with spontaneous ICH, a baseline severity score might be reasonable to provide a general framework for communication with the patient and their caregivers.[472,473] |
| 3: No Benefit | B-NR | 3. In patients with spontaneous ICH, a baseline severity score should not be used as the sole basis for forecasting individual prognosis or limiting life-sustaining treatment.[475,476] |

### *Synopsis*

In the past 2 decades, baseline measures of ICH severity have been developed and tested. Measures such as the ICH score have increasingly been validated in multiple independent cohorts across a range of patient and ICH characteristics. Their precise role in clinical practice has not been fully clarified.

### *Recommendation-Specific Supportive Text*

1. Several baseline measures of ICH severity have been developed and tested in independent populations. Foremost among these is the ICH

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*Stroke.* 2022;53:00–00. DOI: 10.1161/STR.0000000000000407

score, although modifications of the original ICH score[472,473] and other scores also have been developed.[474] The Max-ICH score was developed in particular to minimize confounding by early care limitation and has been validated as superior to the ICH score among patients with ICH who do not have early withdrawal of life-sustaining treatment.[477,478] Most baseline severity scores incorporate patient (eg, age), ICH (eg, anatomic location), and clinical deficit (eg, GCS score) characteristics. In acute neurological injury and critical illness, early assessment of disease severity can help risk-stratify patients. This risk stratification can be useful for quality care metrics and for clinical trial selection.

2. Several recent systematic meta-analyses have quantified the validity of the ICH score for prediction of mortality and functional outcome.[472,473] These data show excellent performance of established severity scores and demonstrate their potential usefulness for risk stratification, assessment of disease severity, adjustment in quality measures, and communication between clinicians and patients and family members. Baseline prognostic scores are often obtained within the first 24 hours, although the optimal timing has not been thoroughly studied.
3. It is important to note that several complementary analyses also highlight the potential limitations of overusing such severity scores, especially in a high-mortality disease with inherent prognostic uncertainty. Many analyses are based on real-world data sets in which management decisions are based on prognosis formation. To the extent that prognostication is informed by severity scores and such prognostication influences management decisions, the potential for a self-fulfilling prophecy exists. In 1 such analysis,[476] ICH prognostic model performance was altered when subjects were stratified according to early DNAR status. Similarly, another prospective analysis found that the subjective judgment of clinicians may correlate more closely to 3-month clinical outcomes compared with the existing scores.[475]

### *Knowledge Gaps and Future Research*

- The application of other baseline biomarkers (imaging, fluid, or electrophysiology based) to outcome prediction remains to be determined. Further investigation is needed of the utility of and best practices for using severity scores in patient/caregiver communication and shared decision-making.
- The role of severity scores in adjustment for hospital- and system-level quality measures of ICH care is unclear and requires further study.
- The use of baseline severity scores in stratification for care decisions or placement in clinical trial strata requires further investigation.
- The concept of patient frailty, increasingly studied as a predictor of disease outcome for elderly individuals, has not yet been incorporated into prediction of ICH outcome.
- The trajectory of ICH recovery and the consequent optimal time for assessing ICH outcome require further study.

## 7.2. Decisions to Limit Life-Sustaining Treatment

**Recommendations for Decisions to Limit Life-Sustaining Treatment**
**Referenced studies that support recommendations are summarized in Data Supplement 70.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-NR | 1. In patients with spontaneous ICH who do not have preexisting documented requests for life-sustaining therapy limitations, aggressive care, including postponement of new DNAR orders or withdrawal of medical support until at least the second full day of hospitalization, is reasonable to decrease mortality and improve functional outcome.[479–484] |
| 2a | C-LD | 2. In patients with spontaneous ICH who are unable to fully participate in medical decision-making, use of a shared decision-making model between surrogates and physicians is reasonable to optimize the alignment of care with patient wishes and surrogate satisfaction.[485] |
| 3: Harm | B-NR | 3. In patients with spontaneous ICH who have DNAR status, limiting other medical and surgical interventions, unless explicitly specified by the patient or surrogate, is associated with increased patient mortality.[180,479,486,487] |

### *Synopsis*

Most patients with ICH who die in the hospital do so after decisions are made by physicians and surrogate decision makers to limit the use of life-sustaining therapies such as artificial nutrition or hydration, intubation and mechanical ventilation, antibiotics, or vasopressors. These decisions are presumably made because of a low likelihood of favorable outcome and alignment with wishes of patients and their legally authorized surrogates (most often their family). However, substantial uncertainty remains concerning the accuracy of prognostication, especially early after ICH onset. When a patient who was destined to recover from their ICH has limitations of life-sustaining therapies or withdrawal of life support, this results in a self-fulfilling prophecy of poor outcome. Numerous studies have found that care limitations in the form of withdrawal of medical support or institution of DNAR orders are independently associated with increased risk of mortality and may lower the likelihood of favorable functional outcome when they are instituted early (usually within the first day) after ICH onset.[479,484,488] Therefore, recommendations are made about the use and intent of these care

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limitations and the process of shared decision-making between surrogates and physicians. Issues considered in this section intersect with outcome prediction and prognostication[476,489] (Section 7.1, Outcome Prediction, and Section 9.1.1, Prognostication of Future ICH Risk). All recommendations should be considered within the relevant cultural, religious, and legal settings in which they are to be applied.

### *Recommendation-Specific Supportive Text*

1. To avoid the self-fulfilling prophecy of poor outcome during a time period in which prognostic uncertainty is present, initial aggressive guideline-concordant care for all patients with ICH (as described in this document) is recommended unless patients have previously documented a desire for these treatment limitations before the onset of their ICH. Most studies that have considered the impact of these treatment limitations have evaluated their institution within the first day after ICH onset because this indicates that one of the earliest decisions in the care of a patient was to limit that care.[479,480,484] However, the optimal and sufficient duration of a trial of aggressive treatment remains uncertain and may extend substantially beyond the second day of hospitalization; 1 study found a lower rate of mortality and higher-than-expected favorable functional outcome with an approach of aggressive care without DNAR orders for at least 5 days.[481] DNAR orders also may be used differently in various cultures.[483] Furthermore, physicians should ensure careful assessment of reversible confounders such as sedation, hydrocephalus, and delirium in considering institution of treatment limitations.[482] For ethical reasons, it seems unlikely that the issue of early treatment limitations will be evaluated in a randomized clinical trial.
2. As a result of neurological impairment, many patients with ICH are unable to participate in discussions about goals for their medical care. Patients ideally will have provided written documentation, or at least informal verbal description, to guide their families and physicians in making decisions that are faithful to their wishes. Even with these patient wishes known, decision-making and implementation are often challenging. The use of a shared decision-making model, in which clinicians ensure the surrogates' understanding, listen to their responses, and incorporate this information into decisions, is encouraged in critical care, but there is very limited ICH-specific published experience. One study found that surrogate satisfaction was associated with greater use of a shared decision-making model.[485] It is unlikely that randomized trials will be conducted with treatment arms that avoid shared decision-making. Thus, the LOE may remain limited, but shared decision-making can reasonably be considered good clinical practice.
3. Medical orders for DNAR status are specific in that they would apply solely in the event of a cardiac or pulmonary arrest (depending on the nature of the order). However, numerous studies have identified that DNAR orders often affect other aspects of care and may lead to less aggressive care in the form of lower likelihood of admission to a stroke unit, less use of guideline-concordant care for VTE prophylaxis, fewer surgical procedures, earlier institution of end-of-life care, and increased mortality.[180,479,486,487] DNAR orders may be unique in this aspect because other orders such as those to administer a medication or perform a surgical procedure apply solely to that specific aspect. Because of the association of DNAR orders with both less aggressive care beyond resuscitation efforts and higher mortality, it is recommended that DNAR orders should apply narrowly to the purpose of the order itself. As with other aspects of this section, this issue is unlikely to be the subject of a randomized clinical trial. Decisions to limit other aspects of care such as specific medical or surgical treatments should be part of shared decision-making discussions between surrogates and physicians.

### *Knowledge Gaps and Future Research*

- The sufficient and optimal duration for a time-limited trial of aggressive therapy to clarify prognosis and avoid the self-fulfilling prophecy of poor outcome is not known and may be substantially longer than several days. Emerging research on coma and recovery of consciousness may have major effects on our understanding of the adequate timing of treatment decisions. Studies in cultures and regions that do not undertake early treatment limitations also may provide insight.
- Studies of overall aggressiveness of care may be more valuable than just limiting DNAR orders. Future development of proxies that measure aggressiveness or guideline-concordant care would be of potential value.
- The impacts of decisional regret, change in lifestyle, and psychological outcomes such as depression, anxiety, and happiness are understudied in surrogate decision makers for patients with ICH. Future studies should include patient- and family-centered measures rather than being limited to just individual patient neurological function. These studies also should seek to identify shared decision-making and communication methods that optimize patient- and family-centered outcomes. Another understudied participant in this process is

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the treating clinician, who might experience stress attributable to either perceived inappropriate life-sustaining treatment or perceived inappropriate early withdrawal of life-sustaining treatment.

# 8. POST-ICH RECOVERY, REHABILITATION, AND COMPLICATIONS

## 8.1. Rehabilitation and Recovery

**Recommendations for Rehabilitation and Recovery**
**Referenced studies that support recommendations are summarized in Data Supplement 71.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with spontaneous ICH, multidisciplinary rehabilitation, including regular team meetings and discharge planning, should be performed to improve functional outcome and reduce morbidity and mortality.[231,232] |
| 1 | A | 2. In patients with spontaneous ICH with mild to moderate severity, early supported discharge is beneficial to increase the likelihood of patients living at home at 3 months.[490] |
| 2b | B-R | 3. In patients with spontaneous ICH with moderate severity, early rehabilitation beginning 24 to 48 hours after onset (including ADL training, stretching, functional task training) may be considered to improve functional outcome and reduce mortality.[491,492] |
| 3: No Benefit | A | 4. In patients with spontaneous ICH without depression, fluoxetine therapy is not effective to enhance poststroke functional status.[493–497] |
| 3: Harm | B-R | 5. In patients with spontaneous ICH, very early and intense mobilization within the first 24 hours is associated with lower likelihood of good recovery.[498,499] |

### *Synopsis*

Stroke rehabilitation includes a number of tailored measures from different professionals with different intensity that depends on individual patient needs and time since stroke. The outcome of rehabilitation is thought to be a combination of recovery attributable to reorganization in the brain and compensatory strategies. To improve multidisciplinary teamwork on the ward, weekly team meetings to discuss patient discharge and appropriate timing are important and improve functional outcome. Starting rehabilitation after 24 to 48 hours after stroke onset seems beneficial; however, intense and frequent mobilization within the first 24 hours is not recommended. Early supported discharge allows care and services to be transferred from the hospital to the home (community setting) and improves the likelihood for independent living. Brain plasticity is the ability of neural networks in the brain to alter through expansion and reorganization, and fluoxetine has been tried in animals with promising results. However, in patients after stroke, it does not improve recovery. We note that much of the data on recovery and rehabilitation come from studies of all types of stroke and mention data from ICH subgroups when available.

### *Recommendation-Specific Supportive Text*

1. Stroke unit care is a model in which a multidisciplinary team of stroke specialists looks after patients with stroke in hospital. The components include[500] structured assessment procedures, coordinated multidisciplinary team care with regular meetings (at least weekly in many of the studies, although the optimal timing has not been defined), and early assessment for planned discharge. This leads to improved functional outcome and reduces mortality independently of patient age, sex, initial stroke severity, and stroke type.[232]
2. Many patients with mild to moderate disability (eg, mRS score ≤3) after ICH can benefit from early supported discharge.[490] This allows patients to continue their rehabilitation therapy at home, with intensity and expertise similar to that of the rehabilitation they would receive in hospital. Early supported discharge not only reduces hospital time but also increases the likelihood that the patient will continue living at home independently compared with those who have had their rehabilitation as inpatients. Early supported discharge also improved the patient-therapist partnership and motivated patients by focusing on realistic rehabilitation goals in the more relevant context of home living and management. This has been shown to work in different countries with different health care systems (Sweden,[501] Canada,[502] Australia,[503] Norway,[504] Thailand,[505] Northern Ireland[506]).
3. Studies generally support early institution of rehabilitation activities. In a Chinese study[492] that compared early rehabilitation as an add-on to usual care, family members were instructed to perform basic rehabilitation (exercises of daily living, stretching exercises, neuromuscular electric stimulation, and functional training such as grasping and pointing) starting within 48 hours of ICH. The study randomized 243 patients (excluding those with either severe or minor deficits) and showed that the intervention resulted in improved survival and functional outcome at 6 months. A multicenter, international study[491] with >11 000 patients with acute stroke (15% ICH) compared lying-flat position to a sitting-up position with the head elevated to at least 30° for the first 24 hours. Lying flat to improve cerebral perfusion was not associated with benefit for the primary outcome, mRS score at 90 days.
4. The concept of enhancing brain plasticity through use of selective serotonin reuptake inhibitors (SSRIs) has been suggested by animal model studies.[495] However, multiple studies of fluoxetine, in either patients with ICH or patients with stroke in general, have not shown beneficial effects on

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functional outcome.[493–497] Patients allocated fluoxetine were less likely to develop new depression by 6 months than patients on placebo but were more prone to fractures.

5. A trial of very early mobilization (AVERT [A Very Early Rehabilitation Trial) compared frequent, higher-dose, and very early mobilization with usual care in 2104 patients with stroke, of whom 258 (12%) had ICH.[499] The intervention was defined as a standardized treatment beginning within 24 hours of stroke onset, focusing on sitting, standing, and walking and resulting in at least 3 additional out-of-bed sessions compared with usual care (increase intensity). The study included >2100 patients in 5 countries and showed that the intervention increased the risk of poor outcome at 3 months. A prespecified subanalysis in patients with ICH showed that this early and intense intervention led to an increased risk of mortality at 14 days after stroke.[498]

### *Knowledge Gaps and Future Research*

- An area for future study is patients' return to work, driving, and participation in other meaningful social activities. The current literature in this area is based largely on epidemiological studies. Greater independence in ADLs, fewer neurological deficits, and better cognitive ability were the most common predictors of return to work. More studies are needed to investigate how vocational rehabilitation should be performed and the role of occupational/vocational therapy in this process.
- There is a knowledge gap from the professionals' side concerning sexual life after ICH, contributing to the infrequency of this topic being addressed in the conversation with patients. Many people fear returning to sexual activity after stroke. However, it seems as though intercourse increases BP only slightly (up to ≈140 mm Hg) for a short time, and then it recovers to baseline level soon after sexual activity in healthy adults.
- There is a lack of knowledge about physical training after ICH. For example, it is unclear how to guide people after ICH in terms of weight lifting (lifts using large muscle groups versus small, heavy lifts versus repetitive lifts) and how much and how long to raise their BP. Furthermore, it is unclear what to advise about any potential bleeding risk related to exertion when BP gets >300 mm Hg.
- There are insufficient data on medications to improve post-ICH functional outcome. Neurostimulants, for example, have not been studied extensively for recovery of consciousness or other recovery steps after ICH.
- Another emerging recovery modality that should be studied after ICH is remote video administration of rehabilitation activities (telerehabilitation).

## 8.2. Neurobehavioral Complications

**Recommendations for Neurobehavioral Complications**
**Referenced studies that support recommendations are summarized in Data Supplements 72 and 73.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. In patients with spontaneous ICH and moderate to severe depression, appropriate evidence-based treatments including psychotherapy and pharmacotherapy are useful to reduce symptoms of depression.[507,508] |
| 1 | B-NR | 2. In patients with spontaneous ICH, administration of depression and anxiety screening tools in the postacute period is recommended to identify patients with poststroke depression and anxiety.[509] |
| 1 | B-NR | 3. In patients with spontaneous ICH, administration of a cognitive screening tool in the postacute period is useful to identify patients with cognitive impairment and dementia.[510] |
| 2a | B-NR | 4. In patients with spontaneous ICH and cognitive impairment, referral for cognitive therapy is reasonable to improve cognitive outcomes.[511–515] |
| 2a | B-NR | 5. In patients with spontaneous ICH and preexisting or new mood disorders requiring pharmacotherapy, continuation or initiation of SSRIs after ICH can be beneficial for the treatment of mood disorders.[508,516–518] |
| 2b | C-LD | 6. In patients with spontaneous ICH and cognitive impairment, treatment with cholinesterase inhibitors or memantine might be considered to improve cognitive outcomes.[519–521] |

### *Synopsis*

Mood disturbances and cognitive dysfunction are common consequences after ICH. Poststroke depression occurs in 20% to 25% of patients with ICH within the first year after stroke,[522] and this persists over time.[523] Thirty-three percent of patients with ICH experience dementia either before or after their ICH,[524] and the incidence of post-ICH dementia increases over time, with 1 study showing an incidence of new-onset dementia of 14.2% at 1 year, increasing to 28.3% at 4 years.[525] Another study noted 32% prevalence of cognitive impairment at 3 years after stroke.[526] Analysis of neuroimaging features of patients who develop post-ICH dementia suggests underlying CAA as a contributing factor.[525] Neurobehavioral complications after ICH are underrecognized by clinicians, leading to worsened long-term patient-centered outcomes such as independence and community reintegration.[527] Poststroke depression is associated with increased short- and long-term mortality[528–532] and poor functional outcomes[532–534] and leads to greater physical limitations, which can impair rehabilitative efforts.[535]

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Poststroke depression also can lead to suicide, which is twice as high in the first 2 years after stroke compared with the general population.[536] Similarly, cognitive impairment predicts poststroke disability[526,535,537] and mortality.[537–539] There is also an interaction between the two: Cognitive symptoms can be caused by depression, and depression can interfere with cognitive function. Recognition and treatment of these stroke complications can have a large impact on stroke recovery.

### *Recommendation-Specific Supportive Text*

1. Patients with poststroke depression and anxiety should be referred to a mental health professional for consideration of psychotherapy or talking-based therapy because several meta-analyses have shown a significant improvement in depression scores[540,541] and remission of poststroke depression[540,541] in patients who underwent psychotherapy with or without pharmacotherapy. Psychotherapy also significantly reduces poststroke anxiety.[542] Pharmacological therapy is beneficial in reducing poststroke depression and anxiety prevalence and symptoms.[540,542–548] Three of the randomized trials evaluating fluoxetine for motor recovery after stroke showed reductions in poststroke depression when fluoxetine was started 2 to 15 days after ischemic stroke or hemorrhagic stroke.[493,496,549] Several studies suggest that transcranial magnetic stimulation also reduces symptoms of poststroke depression.[544,550]
2. Validated screening tools to evaluate for depression and anxiety can lead to improved patient outcomes. One prospective RCT found a significant improvement in depression symptoms for patients with acute ischemic stroke when screening was paired with an Activate-Initiate-Monitor intervention, where Activate represents patient recognition of depression, Initiate represents antidepressant medication, and Monitor represents treatment.[551] In a meta-analysis, Meader and colleagues[509] evaluated the Center for Epidemiological Studies Depression Scale, Hamilton Depression Rating Scale, and Patient Health Questionnaire-9. All had optimal receiver-operating characteristics curves to detect poststroke depression and anxiety. Therefore, any of these screening tools can be used to assess for post-ICH mood disorders. Although many studies report poststroke depression during hospitalization and rehabilitation, mood disorders recur over time. For patients who developed poststroke depression, recurrence increased from 28% in year 2 to 100% by year 15.[529] Although the optimal timing and frequency of depression screening are uncertain, screening should occur not only at transition points across the continuum of care (eg, hospitalization to inpatient rehabilitation) but also in the outpatient setting, especially for patients with a history of poststroke depression within the first year after ICH.[529]
3. Multiple tests are available to screen for cognitive impairment. A meta-analysis compared studies evaluating the Mini-Mental State Examination, Montreal Cognitive Assessment, Rotterdam–Cambridge Cognition Examination, and Addenbrooke's Cognitive Examination–Revised and showed that all demonstrated similar accuracy to detect cognitive impairment and dementia.[510] The Montreal Cognitive Assessment has a high specificity and was shown in 1 study to be the most valid and clinically feasible tool across a wide range of cognitive impairment,[507] but it has a lower specificity for screening.[510,552] The Depression, Obstructive Sleep Apnea, and Cognitive Impairment screening tool takes <5 minutes to administer and may be more practical for assessment of multiple conditions in an outpatient clinic appointment.[527,553] Because there is no superior screening test, consideration should be given to feasibility and level of concern for cognitive impairment in the selection of a particular test. Timing of initial screening is uncertain. Delirium often confounds cognitive assessment during inpatient admission but is associated with posthospital cognitive impairment and reduced quality of life.[554,555] The patient's family and caregivers should be included in the assessment. Evidence shows that dementia continues to develop after ICH; thus, screening should occur across the continuum of inpatient care and at intervals in the outpatient setting. Although detection of post-ICH cognitive impairment is likely to be useful information for the patient's family and care team, it should be noted that current treatments for cognitive impairment appear to have no more than modest benefits.
4. Cognitive therapy, broadly defined as standardized tasks designed to engage, maintain, and improve a patient's thinking skills, has shown mild to modest benefits in improving overall cognitive function for patients with dementia in multiple meta-analyses.[511,515,556,557] The quality of evidence in these studies is hampered by heterogeneity in the types and length of treatment and severity of dementia and a lack of standardization of rehabilitative interventions. In patients with stroke with dementia, the benefits of cognitive therapy have been less clear, with meta-analyses showing uncertain benefits in improvement of attention deficits,[513] memory deficits,[514] and executive dysfunction.[512] The potential benefits of cognitive therapy for post-ICH dementia have not been well established, but given the potential benefits based on a generalized dementia population and lack of side effects, it is reasonable

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to refer patients with ICH with cognitive impairment or dementia for cognitive therapy.

5. The use of SSRIs is beneficial to reduce symptoms of depression and anxiety after stroke.[508,558] Specific caution should be used when initiation of SSRI therapy in an ICH population is considered. Several meta-analyses have shown a small but increased risk of ICH with the use of SSRIs,[508,516,517,559] especially in patients who are taking anticoagulation and strong SSRIs.[508,559,560] This can translate into worsened 3-month neurological outcome.[518] Conversely, 4 randomized trials that evaluated the use of fluoxetine for stroke motor recovery did not show an increased risk of hemorrhagic stroke compared with placebo.[493,494,496,536,549] In patients with ICH, SSRIs should therefore be reserved for patients with moderate to severe depression to balance the importance of treating depression with the risk of increased hemorrhage.
6. There have been no specific trials of treatment of ICH-related cognitive impairment and dementia, but pharmacological therapy has been shown to be beneficial in other types of dementia and cognitive impairment. In the most recent Cochrane reviews, use of memantine has shown a beneficial effect on cognitive function, ADLs, and mood in patients with moderate to severe Alzheimer disease and an improvement in cognitive function, behavior, and mood in mild to moderate vascular dementia,[521] with side effects such as headaches and dizziness. The cholinesterase inhibitor donepezil has been shown more consistently to improve cognitive function and ADLs in patients with vascular cognitive impairment and all levels of Alzheimer dementia,[519,520] with significant side effects such as nausea, diarrhea, anorexia, and cramps. Therefore, it may be reasonable to consider using cholinesterase inhibitors for mild to moderate dementia and memantine for moderate to severe dementia after ICH.

### *Knowledge Gaps and Future Research*

- Further research is needed to determine the optimal screening tools, timing, and frequency of screening for post-ICH depression, anxiety (generally less studied than depression), and cognitive impairment. Given concerns that screening can take time in a busy outpatient practice, rapid screening tools should be developed and validated to ensure identification of these important neurobehavioral consequences of ICH.
- There is a paucity of data on risk of ICH for specific SSRI medications or distinguishing risk profiles between SSRIs and other antidepressant classes such as serotonin-norepinephrine reuptake inhibitors, leading to uncertainty about individual medication choices in patients with ICH who require pharmacotherapy for the treatment of depression. The relative risks and benefits of SSRI or serotonin-norepinephrine reuptake inhibitor use in the ICH survivor population with depression require further prospective evaluation.
- It is unclear whether the same pharmacological agents used to treat Alzheimer dementia, vascular dementia, and cognitive impairment are beneficial to treat post-ICH cognitive impairment. This is an area of future research.

# 9. PREVENTION

## 9.1. Secondary Prevention

### *9.1.1. Prognostication of Future ICH Risk*

**Recommendations for Prognostication of Future ICH Risk**
**Referenced studies that support recommendations are summarized in Data Supplement 74.**

| COR | LOE | Recommendation |
|---|---|---|
| 2a | B-NR | 1. In patients with spontaneous ICH in whom the risk for recurrent ICH may facilitate prognostication or management decisions, it is reasonable to incorporate the following risk factors for ICH recurrence into decision-making: (a) lobar location of the initial ICH; (b) older age; (c) presence, number, and lobar location of microbleeds on MRI; (d) presence of disseminated cortical superficial siderosis on MRI; (e) poorly controlled hypertension; (f) Asian or Black race; and (g) presence of apolipoprotein E ε2 or ε4 alleles.[562–571] |

### *Synopsis*

Survivors of ICH are at risk for hemorrhage recurrence. The estimated recurrence risk ranges from 1.2%/y to 3%/y across undifferentiated patients with ICH, with the highest event rate in the first year after the incident hemorrhage.[562,565–571] However, the individual risk of recurrence can vary considerably according to the underlying pathogenesis (resulting from the higher recurrence rates for ICH associated with CAA relative to arteriolosclerosis), demography, and overall clinical context. A pooled analysis of 325 individuals with ICH diagnosed as attributable to CAA found a recurrence risk of 7.4%/y (95% CI, 3.2%/y–12.6%/y), substantially greater than in the 981 individuals diagnosed with non–CAA-related ICH (recurrence rate, 1.1% [95% CI, 0.5%–1.7%]).[564] Clinical assessment and laboratory testing, including MRI, are helpful for recurrent ICH risk stratification and optimal overall vascular management. A careful assessment of individual recurrence risk may be warranted because patients with ICH are also at risk of ischemic stroke and other major vascular events.[571] In such scenarios, antithrombotic medications are often contemplated, and the risk of hemorrhage must be weighed against the risk of ischemic

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and vaso-occlusive disease. (The complex decision-making process for incorporating this information is addressed in Section 9.1.3, Management of Antithrombotic Agents.)

### Recommendation-Specific Supportive Text

1. Radiological features suggestive of underlying amyloid angiopathy are associated with the highest risk of ICH recurrence. These include a prior lobar ICH (HR, 4.8),[572] the presence of microbleeds[27,573,574] (in particular strictly lobar microbleeds),[27,575] the number of lobar microbleeds (HR, 1.88 for 1 microbleed, 2.93 for 2–4 microbleeds, 4.12 for >4 microbleeds),[572] and the presence of disseminated cortical siderosis (HR, 4.69).[576,577] The presence of microbleeds and cortical siderosis can be determined during the etiological workup of ICH (Section 4.1, Diagnostic Assessment of Acute ICH Course). Carriers of apolipoprotein E genotypes associated with amyloid angiopathy are similarly at higher risk of ICH recurrence compared with those with the more common ε3/ε3 genotype; those with the ε2 or ε4 allele have an HR of 3.3 and 2.5 for recurrence, respectively.[578] Recurrence risk also increases with higher measured outpatient BP[563] and age[570,579] (HR, 2.8 in age >65 years) and is higher in those of Black race (HR, 1.22) or Asian race (HR, 1.29) compared with White race (race defined by self-designation, clinicians, or administrative personnel while in hospital).[568] Association of ICH recurrence with Hispanic ethnicity has been inconsistent.[568,580]

### Knowledge Gaps and Future Research

- There is insufficient evidence to estimate ICH recurrence risk on an individual-patient basis. Deriving and validating a prediction rule incorporating clinical, radiological, and genotype biomarkers and determining the most informative thresholds for categorizing these factors would be helpful to estimate the risk of recurrence.
- The mechanism by which race is associated with ICH recurrence, including the likely crucial role of social determinants of health, is unclear. More research into this association is required.
- MRI findings suggestive of small vessel disease may reflect an increased risk for ICH recurrence. More research is needed into the recurrence risks associated with T2 hyperintensities, enlarged perivascular spaces, microangiopathic changes, intragyral hemorrhage, and lobar versus nonlobar microbleeds.

## 9.1.2. BP Management

**Recommendations for BP Management**
**Referenced studies that support recommendations are summarized in Data Supplements 75 and 76.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. In patients with spontaneous ICH, BP control is recommended to prevent hemorrhage recurrence.[563,581] |
| 2a | B-NR | 2. In patients with spontaneous ICH, it is reasonable to lower BP to an SBP of 130 mm Hg and diastolic BP (DBP) of 80 mm Hg for long-term management to prevent hemorrhage recurrence.[581,582] |

### Synopsis

Hypertension has a strong causal association with ICH and is a major modifiable risk factor for all stroke subtypes. Uncontrolled hypertension accounts for 73.6% of the global population-attributable risk for ICH.[93] Despite this, a significant proportion of ICH survivors continue to have poorly controlled BP.[563,583] Moreover, patients with ICH are also at risk of future ischemic stroke and cardiovascular disease because of overlapping risk factors. Treating hypertension after ICH is a safe and effective way to mitigate future ICH risk and reduce events across the spectrum of vascular disease.[581] It is therefore critical to measure and identify uncontrolled hypertension after ICH and aggressively manage BP to prevent recurrence.

### Recommendation-Specific Supportive Text

1. In a large prospective cohort study of 1145 patients with primary ICH and a median follow-up of 36.8 months, inadequate BP control was associated with increased risk of both lobar (HR, 3.53 [95% CI, 1.65–7.54]) and nonlobar (HR, 4.23 [95% CI, 1.02–17.52]) ICH recurrence.[563] In PROGRESS (Perindopril ProtectionAgainst Recurrent Stroke Study), treatment with perindopril and indapamide reduced mean BP by 10.8/4.4 mm Hg in patients enrolled with ICH and resulted in a relative risk reduction of 42% (95% CI, 14–60) in major vascular events and a number needed to treat of 18 to prevent ICH recurrence over 5 years.[581] The optimal timing for BP lowering after ICH is not known, and a decision to initiate antihypertensive therapy in the acute setting should be in accordance with the recommendations discussed in Section 5.1, Acute BP Lowering.
2. In the PRoFESS trial (Prevention Regimen for Effectively Avoiding Second Strokes), the risk of ICH during follow-up was higher in subjects with SBP ≥160 mm Hg compared with those with SBP of 130 to 139 mm Hg (HR, 2.07 [95% CI, 1.22–3.51]), with a nonsignificant trend toward lower rates of ICH with SBP <130 mm Hg. Similarly, the risk of ICH was higher in subjects with DBP ≥100 mm Hg compared

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with DBP of 80 to 89 mm Hg (HR 2.58 [95% CI, 1.50–4.45]).[582] In a large prospective cohort study of 1145 patients with primary ICH, the risk of ICH recurrence was significantly higher for patients with SBP ≥120 mm Hg and DBP ≥80 mm Hg compared with patients who had SBP <120 mm Hg and DBP <80 mm Hg.[581,584] The relationship between SBP and ICH recurrence was continuous with an HR of 1.33 and 1.54 per 10-mm Hg increase for recurrent lobar and nonlobar ICH, respectively. Although a continuous relationship allows some flexibility with specific BP goals, the ICH evidence supports the ≤130/80-mm Hg target recommended in the 2017 hypertension clinical practice guidelines.[585]

### Knowledge Gaps and Future Research

- The ideal target BP to prevent ICH recurrence is not known. More research is required to determine whether a more aggressive target of SBP of ≤120 mm Hg is beneficial.
- The timing to initiate BP therapy and the optimal class of medication to achieve control are uncertain. Moreover, emerging research suggests that home BP measurements may be a more accurate measure of control. The timing of therapy, best choice of antihypertensive medication, and best approach to outpatient BP monitoring require further study.
- It will be important to determine the predominant factors at the individual, systemic, and societal levels that preclude optimal BP control and identify strategies to overcome these barriers.

## 9.1.3. Management of Antithrombotic Agents

**Recommendations for Management of Antithrombotic Agents**
**Referenced studies that support recommendations are summarized in Data Supplements 77 through 79.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | C-LD | 1. In patients with spontaneous ICH and conditions placing them at high risk of thromboembolic events, for example, a mechanical valve or LVAD, early resumption of anticoagulation to prevent thromboembolic complications is reasonable.[586,587] |
| 2b | B-R | 2. In patients with spontaneous ICH with an indication for antiplatelet therapy, resumption of antiplatelet therapy may be reasonable for the prevention of thromboembolic events based on consideration of benefit and risk.[588,589] |
| 2b | B-NR | 3. In patients with nonvalvular atrial fibrillation (AF) and spontaneous ICH, the resumption of anticoagulation to prevent thromboembolic events and reduce all-cause mortality may be considered based on weighing benefit and risk.[590–595] |
| 2b | C-LD | 4. In patients with AF and spontaneous ICH in whom the decision is made to restart anticoagulation, initiation of anticoagulation ≈7 to 8 weeks after ICH may be considered after weighing specific patient characteristics to optimize the balance of risks and benefits.[596,597] |
| 2b | C-LD | 5. In patients with AF and spontaneous ICH deemed ineligible for anticoagulation, left atrial appendage closure may be considered to reduce the risk of thromboembolic events.[598–602] |

### Synopsis

Antithrombotic therapy is a mainstay of treatment for patients with ischemic cardiovascular or cerebrovascular disease or a history of thromboembolic events. Clinical decision-making concerning the use of antithrombotic medications once these patients have an ICH remains challenging given the paucity of prospective RCTs addressing specific patient populations. Individual patient decisions remain that are based on assessments of risks and benefits of antithrombotic therapies in the context of the published literature of recurrent event rates. Furthermore, data on optimal timing to resume antithrombotic therapy in patients in whom it will be resumed remain sparse. Further discussion of risk factors for recurrent ICH is given in Section 9.1.1, Prognostication of Future ICH Risk. These risks may assist clinicians in patient selection.

### Recommendation-Specific Supportive Text

1. The balance of prothrombotic risks in patients with ICH and an LVAD or mechanical valves with the recurrent hemorrhagic risk of anticoagulation resumption remains challenging. There are sparse data on the risk and timing of device thrombosis versus worsening hemorrhage, and data remain observational. One study found that in patients with LVAD, anticoagulation resumption with warfarin at a median of 14 days from the index ICH was associated with fewer fatal and nonfatal thrombotic events than the resumption of antiplatelet alone, and there was no significant difference in recurrent ICH rates.[586] In an observational study of 22 patients with LVAD with ICH, none had evidence of LVAD thrombosis after reversal and holding of anticoagulation for up to 13 days.[182] In patients with mechanical heart valves, 1 study reported that although complications were significantly increased when anticoagulation was resumed before day 14, the composite of hemorrhage and thromboembolic risk suggested that anticoagulation may be considered in those with mechanical valves as early as day 6 from the index ICH.[587] The decision to restart anticoagulation (eg, at 14 days after ICH for patients with LVAD and potentially earlier for patients with mechanical valves and relatively small ICHs) is therefore reasonable and safe in patients with LVAD or mechanical valves but requires individualized assessment of risk and benefit.
2. The decision to continue antiplatelet therapy in patients with a history of ischemic vascular events who have an incident ICH is challenging given concerns about the risk of ICH recurrence. One open-label RCT addressed this question.[589] In 537 patients randomized at a median of 76 days after ICH onset and followed up for a median of 2 years, treatment with antiplatelet medications led to no increased risk of ICH and a reduction in the composite end point of nonfatal myocardial infarction, nonfatal stroke

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(including ICH and ischemic stroke), and death resulting from a vascular cause. On extended follow-up for up to 7 years, the study found no statistically significant effect of antiplatelet therapy on recurrent ICH or all other major vascular events.[603] These results are consistent with a large meta-analysis of 1916 patients with ICH that reported no significant increase in risk of ICH recurrence and a decreased risk of thromboembolic and ischemic events with resumption of antiplatelet therapy.[588] Important caveats include a scarcity of data on risk differences by location or cause of ICH, lack of blinding, and selection bias in patient enrollment based on clinician assessments of risk. Individual clinician assessment of patients' risks of recurrent ICH and benefits of antiplatelet therapy is needed, but the available data support that, in appropriate patients, the resumption of antiplatelet therapy is reasonable. The optimal timing for resuming antiplatelet therapy has not been systematically studied.

3. A number of retrospective analyses have attempted to address the risks and benefits of anticoagulation therapy in patients with both nonvalvular AF and a history of ICH.[179,590,591,593–595,604] The studies vary by design, including national registries and retrospective and prospective cohorts; have variable inclusion and exclusion criteria and timing to the initiation of anticoagulation; generally study VKA therapy; and include some replication of cohorts across studies. With these limitations, which include systematic differences between anticoagulated and nonanticoagulated individuals attributable to the confounding of choice of therapy by clinician-perceived risk-benefit profile, the published literature suggests a potential reduction in recurrent ischemic events and all-cause mortality with the use of anticoagulation. Anticoagulation may be considered in select patients, based on assessments of risk and benefit, and enrollment in ongoing prospective RCTs should be prioritized to address this clinical dilemma. Given the reduced risk of ICH with DOACs compared with VKAs in stroke prevention trials and real-world practice, these may be favored in patients with a history of ICH if anticoagulation is deemed indicated, although data are lacking.
4. The timing of resumption or initiation of anticoagulation in patients with AF and ICH remains challenging. A study suggests that a composite net benefit of stroke risk reduction and bleeding risk minimization occurs when anticoagulation is started 7 to 8 weeks after ICH.[597] Before 4 to 8 weeks, there appears to be a significant increase in bleeding risk.[596,597] These studies suggest that the optimal timing of initiation of anticoagulation is ≈8 weeks after the index ICH. However, these studies are limited by confounding by indication and clinician and patient preferences. Therefore, timing should be considered on a case-by-case basis of individual risk assessments of thromboembolism, recurrent ICH, and late ICH expansion.
5. Left atrial appendage closure is an alternative in patients with AF and ICH who have contraindications to long-term oral anticoagulation. Two meta-analyses of the PROTECT-AF trial (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL trial (Evaluation of the WATCHMAN Left Atrial Appendage [LAA] Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) reported outcomes in patients randomized to left atrial appendage closure or warfarin therapy.[598,599] Rates of ischemic stroke with left atrial appendage closure did not demonstrate noninferiority compared with warfarin, but rates of hemorrhagic stroke and bleeding were lower, and the primary end point of stroke, systemic embolism, and cardiovascular death was similar across the 2 treatment arms.[598,599] In patients with a history of ICH and AF, data from a small, nonrandomized, retrospective cohort showed lower cardiovascular mortality, all-cause mortality, hemorrhagic stroke risk, and major bleeding events with left atrial appendage closure compared with standard medical therapy.[601] Other small retrospective studies reported low event rates similar to rates in the patients without ICH[600] and no ischemic stroke or ICH within 30 days of left atrial appendage closure among patients diagnosed with CAA.[602] Application of these results to individual patients with ICH remains unclear because of the potential confounding by patient selection, limited numbers of patients reported, and lack of standardization of time interval to left atrial appendage closure, type of antiplatelet or anticoagulant, and duration of treatment before and after implantation.

### *Knowledge Gaps and Future Research*

- In addition to the uncertainty of risk and benefit of anticoagulation in patients with AF and ICH, there is limited evidence for individual selection of optimal timing of anticoagulation resumption in patients for whom anticoagulation will be restarted. Ongoing trials and future studies with stratification based on ICH location, mechanism, and risk factors for recurrence may lead to more informative decisions.
- Most analyses evaluating the role of appropriate antithrombotic therapy in patients with ICH have focused on recurrent events. Future studies that incorporate outcomes such as disability or quality of life in addition to clinical events may provide information that is more patient-centric. More research is also needed on the timing of resumption of antiplatelet therapy and the differences in benefits and

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risks among different agents by different indications and across sex, racial, and ethnic groups.

- Prospective data are lacking on the safety and efficacy of left atrial appendage closure in patients with ICH, particularly when performed within 6 months from the index ICH. This is important given that most patients under consideration for device implantation are under a time-sensitive risk-benefit analysis based on thromboembolic risk of untreated AF. Future studies may need to explore earlier timing and better standardized type and duration of antiplatelet therapy or anticoagulation therapy before and after implantation. As for all device-related therapies, future changes in left atrial appendage closure device type may affect patient outcome.

### 9.1.4. Management of Other Medications

**Recommendations for Management of Other Medications**
**Referenced studies that support recommendations are summarized in Data Supplements 80 and 81.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | B-NR | 1. In patients with spontaneous ICH and an established indication for statin pharmacotherapy, the risks and benefits of statin therapy on ICH outcomes and recurrence relative to overall prevention of cardiovascular events are uncertain.[605–609] |
| 3: Harm | B-NR | 2. In patients with spontaneous ICH, regular long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is potentially harmful because of the increased risk of ICH.[610,611] |

#### Synopsis

Several classes of medications, including SSRIs, statins, and NSAIDs, have the potential for increased risk of recurrent ICH, raising the clinical dilemmas of medication management in patients taking these medications who have an incident ICH. Statin therapy in patients with ICH was associated with an increased risk of recurrent ICH in the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels).[606,612] However, other observational, nonrandomized studies have not found this association in patients with hypercholesterolemia, and risk may depend on the patient risk for recurrent ICH and type of statin used.[607,609,613–618] For both classes of medications, the indications and risk-benefit profiles for an individual patient must be weighed. NSAID use is associated with an increased risk of bleeding[610,611]; thus, regular long-term use should be avoided when possible in patients with ICH. (SSRI use is discussed in Section 8.2, Neurobehavioral Complications.)

#### Recommendation-Specific Supportive Text

1. The association of statin use with both acute outcomes and the reduction of recurrent vascular events in patients who have had an ICH has been uncertain. The SPARCL study identified an increased risk of ICH with high-dose atorvastatin use in the setting of very-low-density lipoprotein levels.[612] Post hoc analyses identified entry into the trial with an ICH as the stroke subtype conveying the highest risk for subsequent ICH but did not find an association between ICH and the most recent pre-ICH low-density lipoprotein value.[606] Additional nonrandomized, observational studies have not found an association with statin use in patients with ICH.[607,609,613,616,618] The risk may be mediated by complex interactions among genetic risk of recurrent ICH, lipid levels, and ICH location.[614,617] In addition, lipophilic statins may be associated with higher rates of ICH than hydrophilic statins.[615] Other retrospective analyses suggest the potential for improved outcomes after ICH with statin use[605,619,620] and a reduction in short- and long-term mortality with statin use.[608,618,621–627] However, the results should be interpreted with caution because of selection bias and confounding by indication in these nonrandomized studies. Given this uncertainty, the decision to use statins in patients with ICH depends on risk assessment of ischemic cardiovascular and cerebrovascular events versus recurrent ICH. Enrollment in ongoing randomized clinical trials addressing this question can be encouraged. Clinical trials of the lipid-lowering PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitors) have thus far not suggested increased risk of first ICH but have not yet examined risk of recurrence in patients with prior ICH.[628–630]
2. The use of NSAIDs is associated with an increased risk of bleeding. Overall event rates of ICH are low in the general population, but a large meta-analysis of observational studies found an increased risk of hemorrhagic stroke with diclofenac and meloxicam use.[611] A subsequent large meta-analysis found an increased risk of ICH with any NSAID use.[610] One small study of patients with ICH with short-term outcomes found no association of NSAID use with outcomes and recurrent ICH, but follow-up was limited to 90 days.[631] Given the increased risk of bleeding with NSAID use, that patients with ICH are at higher risk of recurrent ICH than the general population, and the existence of safer alternatives to NSAID such as acetaminophen for most indications, the regular (eg, daily) use of NSAIDs after an ICH is not recommended, although randomized data and data drawn from individuals with ICH are lacking.

#### Knowledge Gaps and Future Research

- The effect of statins on long-term incident ischemic and hemorrhagic events in patients with ICH is uncertain, as is the effect of statin use on short-term outcomes after ICH. Ongoing and future studies to identify patient populations who may benefit from both short- and long-term statin use or from changing to an alternative lipid-lowering agent such as ezetimibe or a PCSK9i are needed.
- Further research on radiological and biological markers that may further refine risk of recurrence such as MRI markers of cerebral small vessel

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disease, genetic risk, BP, and medication interactions would aid in the risk stratification in patients requiring the use of these medications.

- There is growing but still uncertain evidence that some commonly used medications other than the antithrombotics may increase ICH risk.

### 9.1.5. Lifestyle Modifications/Patient and Caregiver Education

| Recommendations for Lifestyle Modifications/Patient and Caregiver Education<br>Referenced studies that support recommendations are summarized in Data Supplement 82. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| Lifestyle modification | | |
| **2a** | **C-LD** | 1. In patients with spontaneous ICH, lifestyle modification is reasonable to reduce BP.[632] |
| **2a** | **C-LD** | 2. In patients with spontaneous ICH, avoiding heavy alcohol consumption is reasonable to reduce hypertension and risk of ICH recurrence.[633–635] |
| **2b** | **C-LD** | 3. In patients with spontaneous ICH, lifestyle modification, including supervised training and counseling, may be reasonable to improve functional recovery.[636,637] |
| Patient and caregiver education | | |
| **2a** | **C-LD** | 4. In patients with spontaneous ICH, psychosocial education for the caregiver can be beneficial to increase patients' activity level and participation and/or quality of life.[638] |
| **2a** | **C-LD** | 5. In patients with spontaneous ICH, practical support and training for the caregiver are reasonable to improve patients' standing balance.[639] |

#### Synopsis

Lifestyle modifications are part of not only primary but also secondary prevention, an important self-care component of poststroke management. This includes increased physical activity, smoking cessation, reduction in alcohol consumption, and a healthy diet and is positive for overall health.[632,637] These recommendations are beneficial for many so-called noncommunicable conditions, related to an individual's way of life. After the acute hospitalization and rehabilitation period, the family often takes on the role of a caregiver for the patient with ICH after the return to home. To optimize rehabilitation, the caregiver needs to be involved and knowledgeable. Therefore, there is a need for caregiver information about the diseases and what to do and expect. Caregiver interventions include assisting with mobility and ADLs or performing exercise with the patient. This requires practical training of the caregiver, information about assistive devices, and support.

#### Recommendation-Specific Supportive Text

1. There are positive effects from multimodal secondary stroke prevention. Secondary prevention includes increased physical activity, smoking and recreational drug cessation, reduction in alcohol consumption, and a healthy diet.[632,640] A healthy diet contains increased levels of fish rich in long-chain omega-3 fatty acids, vegetables and fruit, and whole-grain products, as well as lower levels of red meat, reduced levels of salt and added sugar, and replacement of saturated fats with polyunsaturated or monounsaturated fats.[641] A meta-analysis[632] showed positive effects in patients with transient ischemic attack and stroke with lower BP, and positive trends were noted in relation to blood lipids and anthropomorphic measures. Many studies were small and of varied quality, and none were studies of patients with ICH.
2. Heavy alcohol consumption can lead to intermittently elevated BP, which is particularly unhealthy in people with a prior ICH.[633,634] For those with large alcohol intake, a reduction by half had the strongest impact on BP.[635] Heavy alcohol consumption[633] or all alcohol consumption[93] is associated with ICH risk in observational studies, although confounding by other lifestyle factors is difficult to exclude.
3. Lifestyle modifications, in particular increased physical activity, might lead to reduced BP.[637,640] Although the mechanism of action is not fully understood, supervised training and counseling seem to have a significant impact on increasing physical activity. Increased physical activity such as reducing sitting time and taking daily walks has an impact, in particular going from sedentary to some activity level. These activities are feasible for many patients after stroke.[636]
4. In patients with stroke, psychosocial education for the caregiver can be beneficial to increase patients' activity level and participation and/or quality of life.[642] Psychosocial interventions reduced depressive symptoms not only in the stroke survivors but also in their caregivers[638] and may lead to reduced anxiety and improved quality of life and coping.[635] This type of intervention was found to be acceptable to caregivers and can be delivered in a group setting and in one-to-one formats.[643] As often in rehabilitation, the question of timing requires tailoring to individual needs. Data supporting the use of psychosocial education have come largely from studies of general stroke but not specifically from patients with ICH.
5. Practical support for the caregiver (such as how to walk safely with the patient) and training (such as how to perform certain exercises) are reasonable and can make performing some rehabilitation exercises at home feasible. This is not as effective as doing exercises with professionals but can lead to improvement in patients' standing balance.[639] Whether this is cost-effective compared with conventional rehabilitation is unclear; however, caregiver burden did not seem to increase. Caregiver-mediated exercise routines may be a promising form of therapy to add to usual care.[639] Several factors limit the interpretation of these studies, however. The data are from studies of patients with general stroke rather than specifically patients with ICH, and the positive associations

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with standing balance are derived from secondary rather than primary outcome analyses.

### *Knowledge Gaps and Future Research*

- There are positive effects of lifestyle modification; however, it is not known how to best target this and make the changes sustainable. The presumption is that tailored interventions are better than standardized interventions, but this needs to be investigated. There is also a lack of knowledge about which components of lifestyle modifications have the highest impact and the optimal frequency and content of outpatient follow-up visits.
- Patient and caregiver education has been shown to be beneficial; however, it is still unclear how this should be delivered.
- Another component of the education of the patient with ICH and caregiver that has not been studied is systematic use of advanced directives to determine preferences in case of recurrent ICH or other major events.

## 9.2. Primary ICH Prevention in Individuals With High-Risk Imaging Findings

**Recommendations for Primary ICH Prevention in Individuals With High-Risk Imaging Findings**
**Referenced studies that support recommendations are summarized in Data Supplements 83 and 84.**

| COR | LOE | Recommendation |
|---|---|---|
| 2b | C-LD | 1. When considering primary prevention of ICH, it may be reasonable to incorporate any available MRI results demonstrating cerebral microbleed burden or cortical superficial siderosis to inform shared decision-making about stroke prevention treatment plans.[25,564,644–648] |

### *Synopsis*

Neuroimaging is not routinely performed as a part of risk stratification for primary (in the sense of first-ever) ICH risk. However, MRI is occasionally available in certain individuals and may reveal markers potentially concerning for future ICH risk. There is a paucity of data from broad populations on neuroimaging markers and risk of first-ever spontaneous ICH. Although clinicians may consider these data when planning potential preventive treatments such as antithrombotic therapy or BP management (see the 2017 hypertension clinical practice guidelines[585]), there are limited data to guide specific practice. Importantly, the absolute risk of primary ICH is many orders of magnitude lower than the risk of secondary (recurrent) ICH and, even in individuals with these markers, is also less than the risk of primary ischemic stroke.[644]

### *Recommendation-Specific Supportive Text*

1. One population-based study in a predominantly White healthy European population demonstrated that cerebral microbleed burden and lobar location were associated with increased risk of future ICH.[644] Observational data in selected hospital-based populations also suggest increased risk associated with cerebral microbleed burden or cortical superficial siderosis. In a retrospective single-center analysis of patients diagnosed with probable cerebral amyloid angiopathy who underwent MRI for clinical symptoms other than ICH (such as cognitive symptoms or transient focal neurological episodes), the presence and extension of cortical superficial siderosis (detected as curvilinear hypo-intensity following the cortical surface and distinct from vessels) predicted subsequent symptomatic ICH.[564,645] In a multicenter patient-level meta-analysis of patients with prior transient ischemic attack or stroke, cerebral microbleed burden was found to be associated with increased risk of ICH[648] and can be incorporated into a risk score for predicting ICH.[649] In a multicenter observational study in patients with prior IS and AF treated with anticoagulation, presence of cerebral microbleed burden increased the risk of ICH.[25] With regard to antithrombotic exposure, several case-control analyses suggest that patients with cerebral microbleed burden are more at risk of developing ICH when treated with warfarin.[646,647] In summary, the current evidence suggests that cerebral microbleed burden, specifically in the lobar location, and multifocal and disseminated cortical superficial siderosis may increase risk profiles.

### *Knowledge Gaps and Future Research*

- Population-based risk assessment with neuroimaging and other markers requires further research and validation.
- Further investigation is needed in understanding the interaction between cardiovascular prevention strategies (eg, antithrombotic use or BP targets) and high-risk neuroimaging markers for ICH.
- Diverse populations should include those with varied racial and ethnic backgrounds, genetic profiles, and preexisting comorbidities.

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## ARTICLE INFORMATION

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### Disclosures

**Appendix 1. Writing Group Relationships With Industry and Other Entities (Relevant)—2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Steven M. Greenberg | Massachusetts General Hospital | None | None | None | None | None | None | None |
| Wendy C. Ziai | Johns Hopkins University School of Medicine | None | None | None | None | None | None | None |
| Charlotte Cordonnier | University of Lille, Lille University Hospital (France) | None | None | Boehringer-Ingelheim* | None | None | Amgen*; Biogen (Steering Committee)*; Bristol Myers Squibb (Steering Committee)* | None |
| Dar Dowlatshahi | University of Ottawa (Canada) | None | None | None | None | CARL (Patent)* | None | None |
| Brandon Francis | Michigan State University | None | None | None | None | None | None | None |
| Joshua N. Goldstein | Massachusetts General Hospital | None | None | None | None | None | Alexion†; CSL Behring†; NControl†; Octapharma*; Pfizer (medical monitor)†; Phillips†; Portola†; Takeda† | None |
| J. Claude Hemphill III | University of California, San Francisco | None | None | None | None | None | None | None |
| Ronda Johnson | Metric Engineering, Inc; real estate consultant | None | None | None | None | None | None | None |
| Kiffon M. Keigher | Advocate Aurora Health System, Park Ridge | None | None | None | None | None | None | None |

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**Appendix 1. Continued**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| William J. Mack | University of Southern California | None | None | None | None | Cerebrotech†; Endostream†; Imperative Care†; Q'Apel†; Rebound Therapeutics†; Spartan Micro†; Stream Biomedical*; Truvic†; Vastrax†; Viseon† | Imperative Care*; Integra†; Q'Apel†; Rebound Therapeutics†; Spartan Micro†; Stream Biomedical*; Stryker* | None |
| J. Mocco | Mount Sinai Health System | None | None | None | None | Cerebrotech†; Corindust†; CVAid*; Echovate†; Endostream†; Imperative Care†; Medtronic†; NTI†; Rebound Therapeutics†; RIST†; Serenity†; Spinaker†; Synchron†; Truvic†; Vastrax† | Cerebrotech†; Endostream†; Imperative Care†; Synchron† | None |
| Eileena J. Newton | Johns Hopkins University | None | None | None | None | None | None | None |
| Ilana M. Ruff | Advocate Aurora, Milwaukee | None | None | None | None | None | None | None |
| Lauren H. Sansing | Yale University School of Medicine | None | None | None | None | None | None | None |
| Sam Schulman | McMaster University (Canada) | Boehringer Ingelheim (PI)†; Octapharma (PI)† | None | Bristol Myers Squibb*; Pfizer* | None | None | None | None |
| Magdy H. Selim | Harvard Medical Faculty Physicians, Beth Israel Deaconess Medical Center | None | None | None | None | None | None | None |
| Kevin N. Sheth | Yale University | Bard (PI)*; Biogen (PI)*; Hyperfin (PI)*; Novartis (PI)* | None | None | None | Alva (Co-Founder)*; Astrocyte (equity)*; Certus (equity)* | CereVasc*; CSL Bering*; Rhaeos* | None |
| Nikola Sprigg | University of Nottingham (United Kingdom) | None | None | None | None | None | None | None |
| Katharina S. Sunnerhagen | University of Gothenburg, Institute of Neuroscience and Physiology; Sahlgrenska University Hospital (Sweden) | None | None | None | None | None | None | None |

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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**Appendix 2. Peer Reviewer Relationships With Industry and Other Entities (Comprehensive): 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage**

| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Opeolu Adeoye | Washington University | NIH/NINDS† | None | None | None | Sense Diagnostics, Inc† | None | Nico Corp, DSMB member† |
| Walter Ageno | Università degli Studi dell'Insubria–Varese | Bayer (to institution)† | None | Pfizer*; Werfen*; Sanofi* | None | None | Bayer*; Leo Pharma*; Sanofi*; Janssen* | None |
| Rustam Al-Shahi Salman | University of Edinburgh | None | None | None | None | None | None | None |
| Sepidah Amin-Hanjani | University of Illinois at Chicago | None | None | None | None | None | None | None |
| Craig Anderson | The George Institute for Global Health, University of New South Wales (Australia) | National Health and Medical Research Council (NHMRC) of Australia†; Medical Research Council (MRC) of UK† | Takeda† | None | None | None | None | None |
| Jeanette Baumann | UCHealth | None | None | None | None | None | None | None |
| Alessandro Biffi | Massachusetts General Hospital/Harvard Medical School | None | None | None | None | None | None | None |
| Torrey Birch | Rush University Medical Center | None | None | None | None | None | Gift of Hope Advisory Board*; legal firm consulting* | None |
| Grégoire Boulouis | Centre Hospitalier Universitaire de Tours (France) | None | None | None | None | None | None | None |
| Ken Butcher | UNSW and NSW Health (Prince of Wales Hospital) (Australia) | None | None | Boehringer Ingelheim*; Pfizer* | None | None | None | None |
| Wendy Camp | Baptist Health | None | None | None | None | None | None | None |
| Andrew Carlson | University of New Mexico | NIH†; DOD† | None | None | None | None | None | None |
| Jean-Louis Caron | Retired | NA | NA | NA | NA | NA | NA | NA |
| Claire J. Creutzfeldt | University of Washington | NINDS† | None | None | None | None | None | None |
| Adam Cuker | University of Pennsylvania | None | None | None | None | None | Synergy CRO† | UpToDate authorship royalties† |
| Barry M. Czeisler | Providence Little Company of Mary Medical Center–Torrance (previously at NYU Langone Health) | American Academy of Neurology* | None | None | 1 case for plaintiff* | None | None | None |
| Nega Dangayach | Mount Sinai | TAAF†; Friedman Brain Institute† | None | None | None | None | Jacobs Institute*; advisor, Lubin Business School Transformative Leadership Program* | None |
| Laura C. Gioia | Université de Montréal (Canada) | None | Fellowship Funding for research project (Servier Inc)† | None | None | None | None | None |

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| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Prasanthi Govindarajan | Stanford University | AHRQ† | None | None | None | None | None | *Stroke, Annals of Emergency Medicine, JAMA Network Open, Academic Emergency Medicine* (Reviewer)* |
| Mark R. Harrigan | University of Alabama, Birmingham | None | None | None | None | None | None | None |
| Theresa Human | Cumberland Pharma | None | None | None | None | None | None | None |
| Hagen Huttner | Universitätsklinikum Giessen (Germany) | Alexion* | None | Alexion* | None | None | None | None |
| David Hwang | Yale School of Medicine | None | None | None | None | None | None | None |
| Susan Kahn | McGill | None | None | None | None | None | Sanofi*; Alexion* | None |
| Richard Kaufman | Harvard Medical School | None | None | None | Scrudder Bass LLC†; Haliczer Pettis Schwam LLC* | None | None | None |
| Karin Klijn | Radboud University Medical Center (Netherlands) | Penumbra Inc† | None | None | None | None | None | None |
| Nerissa Ko | UCSF | None | None | None | None | None | None | None |
| Joji Kuramatsu | University Hospital Erlangen (Germany) | None | None | Biogen* | None | None | None | None |
| Ariane Lewis | NYU Langone Medical Center | None | None | Neurodiem* | None | None | None | *Neurology (Deputy Editor)*; Seminars in Neurology (Deputy Editor)** |
| Vasileios-Arsenios Lioutas | Harvard | None | None | None | None | None | Qmetis* | None |
| Demetrius Lopes | Advocate Aurora Health | None | None | Rapid AI†; Siemens† | None | Methinks†; Viz.AI†; Three Rivers†; Vastrax†; Synchron†; NDI†; Bend it†; NextGEN†; Qupel†; Stryker†; Medtronic†; Asahi† | National PI† | Cerus (Neck trial)†; Medtronic (Vantage trial)† |
| Matthew Maas | Northwestern University | None | None | None | None | None | None | None |
| Elisabeth B. Marsh | Johns Hopkins School of Medicine | NIH†; American Heart Association† | Iorizzo family† | None | None | None | Quality Committee AAN* | *Stroke* (Editorial Board)* |
| Stephan Mayer | Westchester Medical Center Health System | None | None | None | None | None | CSL Behring*; MaxQ AI† | None |
| John Oostema | Michigan State University | None | None | None | None | None | None | None |

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| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Aditya S. Pandey | University of Michigan | NIH†; American Hydrocephalus Association†; Focused Ultrasound Foundation† | None | None | None | NextGen†; FlexDex Surgical† | None | None |
| Terry Quinn | University of Glasgow (United Kingdom) | BMS* | None | None | None | None | NovoNordisk* | None |
| Stacey Quintero Wolfe | Wake Forest School of Medicine | None | None | None | None | None | None | None |
| Venkatakrishna Rajajee | University of Michigan | None | None | None | None | None | None | None |
| Jeff Saver | Geffen School of Medicine at UCLA | NIH-NINDS† | None | None | None | None | Boehringer Ingelheim*; Bayer*; Hoffman-LaRoche* | None |
| Clemens Schirmer | Geisinger | None | Penumbra*; NICO* | None | None | None | None | None |
| Ashkan Shoamanesh | McMaster University (Canada) | Daiichi Sankyo†; Servier Canada Inc†; Bayer AG†; Octapharma* | None | Servier Canada Inc†; Bayer AG*; Daiichi Sankyo* | None | None | Bayer AG†; Daiichi Sankyo* | DSMB Bayer AG† |
| Deborah Siegal | None | None | None | Honoraria: BMS-Pfizer*, Leo Pharma*, Roche*, Servier* | None | None | None | None |
| Daniel Strbian | Helsinki University Hospital (Finland) | None | None | None | None | None | BMS* | None |
| Jeanne Teitelbaum | Montreal University Health Center (Canada) | None | None | None | Medico-legal cases† | None | None | None |
| Stavropoula Tjoumakaris | Jefferson University Hospitals | None | None | None | None | None | Medtronic*; Microvention* | None |
| Mary Traynor | Atrium Health | None | None | None | None | None | None | None |
| Paul Vespa | UCLA | NINDS†; State of California† | Ceribell† | Ceribell†; UCB† | Medico-legal cases† | None | UCB†; Ceribell† | None |
| David Werring | None | None | None | Bayer*; Alexion* | None | None | NovoNordisk* | None |
| Vignan Yogendrakumar | None | None | None | None | None | None | None | None |
| Lori Yokomizo | Hackensack Meridian Health | None | None | None | None | None | None | None |
| Darin Zahuranec | University of Michigan | NIH† | None | None | None | None | None | None |
| Eli Zimmerman | Vanderbilt University Medical Center | None | None | None | None | None | None | None |

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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