

## 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

Steven M. Greenberg, MD, PhD, FAHA, Chair; Wendy C. Ziai, MD, MPH, FAHA, Vice Chair; Charlotte Cordonnier, MD, PhD; Dar Dowlatshahi, MD, PhD, FAHA; Brandon Francis, MD, MPH; Joshua N. Goldstein, MD, PhD, FAHA; J. Claude Hemphill III, MD, MAS, FAHA; Ronda Johnson, MBA; Kiffon M. Keigher, MSN, ACNP-BC, RN, SCRNI; William J. Mack, MD, MS, FAHA\*; J. Mocco, MD, MS, FAHA†; Eileena J. Newton, MD; Ilana M. Ruff, MD‡; Lauren H. Sansing, MD, MS, FAHA; Sam Schulman, MD, PhD; Magdy H. Selim, MD, PhD, FAHA; Kevin N. Sheth, MD, FAHA\*§; Nikola Sprigg, MD; Katharina S. Sunnerhagen, MD, PhD; on behalf of the American Heart Association/American Stroke Association

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

## 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 pathogenesis.
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.

\*AHA Stroke Council Scientific Statement Oversight Committee on Clinical Practice Guideline liaison. †AANS/CNS liaison. ‡AHA Stroke Council Stroke Performance Measures Oversight Committee liaison. §AAN representative.

AHA Stroke Council Scientific Statement Oversight Committee members, see page e\*\*\*.

Supplemental material is available at <https://www.ahajournals.org/doi/suppl/10.1161/STR.0000000000000407>

© 2022 American Heart Association, Inc.

Stroke is available at [www.ahajournals.org/journal/str](http://www.ahajournals.org/journal/str)

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 cardiovascular 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

other entities (RWI) can be found at <https://professional.heart.org/-/media/phd-files/guidelines-and-statements/policies-devolpment/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 non-critical tables and figures.

*Joseph P. Broderick, MD, FAHA  
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),<sup>1</sup> 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  $\approx$ 1.6-fold greater among Black than White people<sup>2</sup> and 1.6-fold greater among Mexican American than non-Hispanic White people.<sup>3</sup> 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.<sup>4,5</sup>

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.<sup>6–9</sup> 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.<sup>8</sup> Another growing source of ICH is more widespread use of anticoagulants,<sup>10</sup> a trend likely to counterbalance the reduced ICH risk associated with increasing prescription of direct oral anticoagulants (DOACs) relative to vitamin K antagonists (VKAs).<sup>11</sup>

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

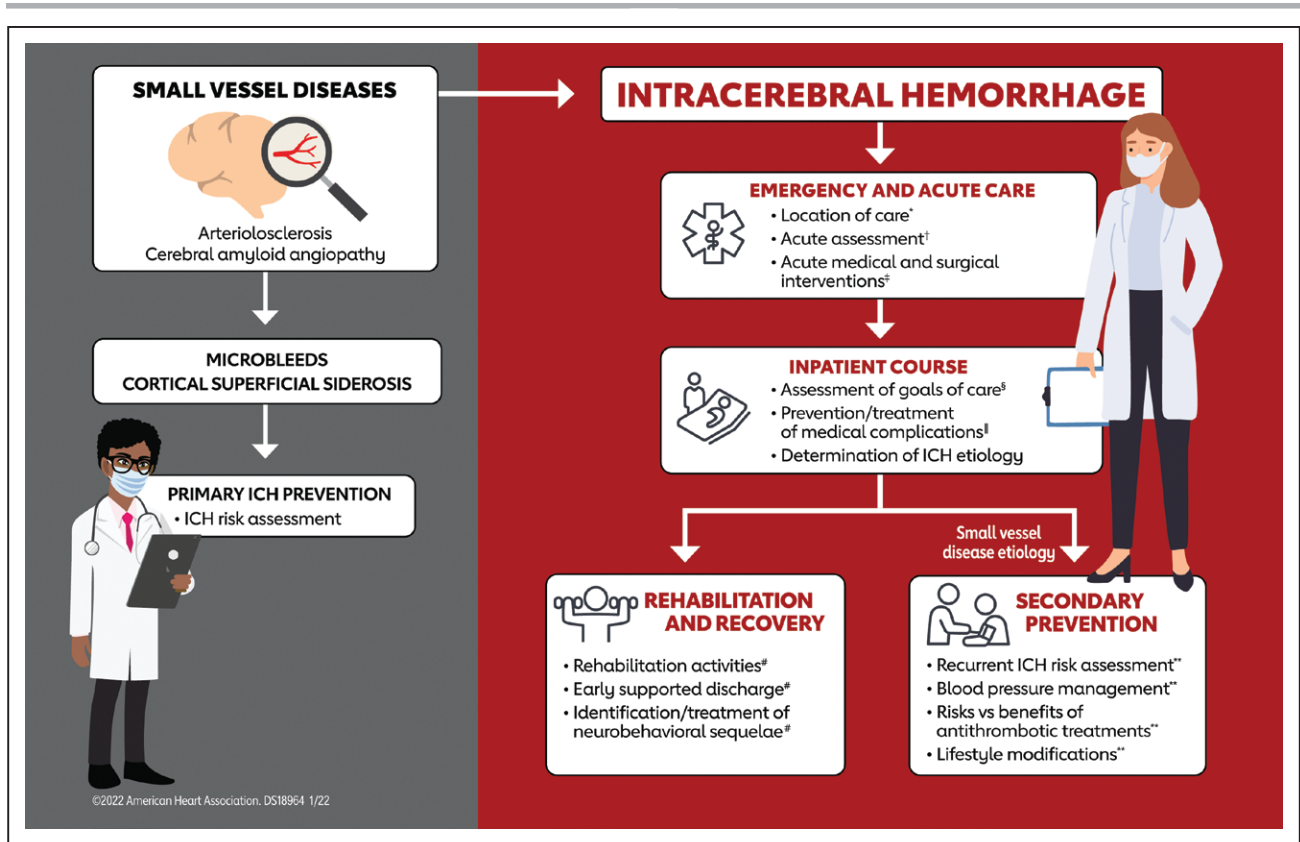
The recommendations listed in this guideline are, whenever possible, evidence based and supported by extensive evidence review. A search for literature derived from research principally involving human subjects, published in English, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected 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](#).



**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.

### 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.<sup>12</sup> 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,<sup>13</sup>

aneurysmal subarachnoid hemorrhage,<sup>14</sup> or unruptured saccular aneurysms.<sup>13,15</sup> 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.<sup>16,17</sup> 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



**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.

(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.<sup>18,19</sup>

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,<sup>20</sup> 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

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

Abbreviation	Meaning/Phrase
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

## 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.<sup>21</sup> 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  $\beta$ -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  $\epsilon$ 2 or  $\epsilon$ 4 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,

**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	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS 1 (STRONG)</b> <span style="float: right;"><b>Benefit &gt;&gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is recommended</li> <li>• Is indicated/useful/effective/beneficial</li> <li>• Should be performed/administered/other</li> <li>• Comparative-Effectiveness Phrases†: <ul style="list-style-type: none"> <li>– Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>– Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>LEVEL A</b> <ul style="list-style-type: none"> <li>• High-quality evidence‡ from more than 1 RCT</li> <li>• Meta-analyses of high-quality RCTs</li> <li>• One or more RCTs corroborated by high-quality registry studies</li> </ul>
<b>CLASS 2a (MODERATE)</b> <span style="float: right;"><b>Benefit &gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is reasonable</li> <li>• Can be useful/effective/beneficial</li> <li>• Comparative-Effectiveness Phrases†: <ul style="list-style-type: none"> <li>– Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>– It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>LEVEL B-R (Randomized)</b> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more RCTs</li> <li>• Meta-analyses of moderate-quality RCTs</li> </ul>
<b>CLASS 2b (WEAK)</b> <span style="float: right;"><b>Benefit ≥ Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• May/might be reasonable</li> <li>• May/might be considered</li> <li>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established</li> </ul>	<b>LEVEL B-NR (Nonrandomized)</b> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>• Meta-analyses of such studies</li> </ul>
<b>CLASS 3: No Benefit (MODERATE)</b> <span style="float: right;"><b>Benefit = Risk</b></span> <b>(Generally, LOE A or B use only)</b> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is not recommended</li> <li>• Is not indicated/useful/effective/beneficial</li> <li>• Should not be performed/administered/other</li> </ul>	<b>LEVEL C-LD (Limited Data)</b> <ul style="list-style-type: none"> <li>• Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>• Meta-analyses of such studies</li> <li>• Physiological or mechanistic studies in human subjects</li> </ul>
<b>Class 3: Harm (STRONG)</b> <span style="float: right;"><b>Risk &gt; Benefit</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Potentially harmful</li> <li>• Causes harm</li> <li>• Associated with excess morbidity/mortality</li> <li>• Should not be performed/administered/other</li> </ul>	<b>LEVEL C-EO (Expert Opinion)</b> <ul style="list-style-type: none"> <li>• Consensus of expert opinion based on clinical experience</li> </ul>

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.<sup>22,23</sup> 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.<sup>24</sup> 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.<sup>25</sup> It is important to note, however, that the small vessel pathologies that underlie ICH are also associated with increased risk of ischemic stroke,<sup>26</sup> 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).<sup>27</sup>

## 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



and cellular pathways triggered by the hematoma and its metabolized blood products.<sup>28</sup> 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,<sup>29</sup> is common and a consistent predictor of worse ICH outcome.<sup>30</sup>

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.<sup>28</sup> 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. <sup>31-35</sup>

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. <sup>36-41</sup>
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. <sup>32,42</sup>
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. <sup>43,44</sup>
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. <sup>45</sup>
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. <sup>46,47</sup>
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). <sup>48,49</sup>

### 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.



## 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.<sup>33</sup> Public education campaigns can improve stroke knowledge,<sup>35,50</sup> increase the use of EMS for stroke,<sup>31</sup> and use of EMS is associated with shorter time to diagnosis.<sup>32</sup> 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.<sup>34</sup> Although some smaller studies have demonstrated modest benefits, others have shown no or only transient benefits.<sup>51–54</sup> Knowledge of stroke warning signs varies by race, sex, ethnicity, age, education, and urbanicity,<sup>33</sup> 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.<sup>41</sup> 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,<sup>37</sup> 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).<sup>36</sup> One group analyzed ICH specifically<sup>39</sup> 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.<sup>40</sup>
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]).<sup>32,42</sup> 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.<sup>55</sup> 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.<sup>56–59</sup> 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.<sup>44</sup> 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.<sup>43</sup> 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).<sup>60</sup>
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]).<sup>45</sup>
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

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.<sup>47</sup> 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.<sup>46</sup> 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.

- 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.<sup>49</sup> 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.<sup>48,61,62</sup> This suggests a value for EMS clinicians trained in performing initial and serial neurological examinations using a stroke screening tool<sup>63–66</sup> 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. <sup>67–72</sup>

#### 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

**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 Thunderclap: Aneurysm, RCVS, some instances of CVST Slower onset: Mass lesion, some instances of CVST, ischemic stroke with hemorrhagic transformation Focal neurologic deficits Seizures Decreased level of consciousness
Vascular risk factors	Ischemic stroke Prior ICH Hypertension (Section 9.1.2) Hyperlipidemia Diabetes Metabolic syndrome Imaging biomarkers (eg, cerebral microbleeds; Section 9.1.1)
Medications	Antithrombotics: Anticoagulants (Section 5.2.1), thrombolytics, antiplatelet agents (Section 5.2.2), NSAIDs (9.1.4), dose and time of last ingestion Vasoconstrictive agents (associated with RCVS): Triptans, SSRIs (Section 8.2), decongestants, stimulants, phentermine, sympathomimetic drugs Antihypertensives (as a marker of chronic hypertension) 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 Alcohol use Marijuana (associated with RCVS) 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. <sup>73,74</sup> Thrombocytopenia is associated with increased mortality. <sup>75</sup> Acute kidney injury and hyperglycemia are associated with worse outcomes and mortality. <sup>68-71,76-81</sup> Inflammatory markers are associated with infective endocarditis. <sup>82</sup> GFR influences clearance of DOACs. <sup>83</sup>
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. <sup>84-86</sup> Specific tests for DOACs (including dilute thrombin time, anti-Xa activity) may be useful for considering reanticoagulation. <sup>87</sup>
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.

complete blood count and coagulation profile can help to diagnose coagulopathy attributable to medications or underlying medical conditions such as hematologic malignancies.<sup>72</sup> 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

- 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.<sup>84–86</sup> Admission anemia is associated with hemorrhagic expansion and poor outcomes<sup>73,74</sup> and thrombocytopenia is associated with higher mortality for patients taking antiplatelets.<sup>75</sup> 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,<sup>88</sup> whereas another showed no association.<sup>89</sup> Elevated troponin on admission for patients with ICH is associated with increased in-hospital mortality for both medical and surgical ICH patient populations.<sup>67,69,90–92</sup> The association of admission troponin with functional outcomes and 30-day mortality was reported in 1 study<sup>67</sup> but not in another study after adjustment for confounding factors.<sup>71</sup> Renal failure on admission also is associated with poor functional outcomes,<sup>71,76,77,79</sup> in-hospital mortality,<sup>80</sup> and 12-month mortality.<sup>76,79</sup> Admission hyperglycemia is associated with unfavorable short- and long-term outcomes,<sup>70</sup> short-term mortality,<sup>68,78,81</sup> and long-term mortality after ICH.<sup>68</sup> Additional lifestyle risk factors that should be assessed include tobacco smoking, diet, alcohol, and waist-to-hip ratio.<sup>93</sup>

### 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. <sup>94–96</sup>
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. <sup>97–99</sup>
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. <sup>100–102</sup>



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. <sup>103-108</sup>
2b	B-NR	5. In patients with spontaneous ICH, using non-contrast computed tomography (NCCT) markers of HE to identify patients at risk for HE may be reasonable. <sup>106</sup>

### Synopsis

Brain imaging is essential to distinguish ICH from ischemic stroke and determine ICH volume (often estimated in practice with the ABC/2 formula<sup>109</sup>). 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.<sup>94,95,110</sup> 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.<sup>30,97,98,111</sup> Identification of a spot sign on CTA or contrast-enhanced CT<sup>104,107,108</sup> or certain imaging features on NCCT such as heterogeneous densities within the hematoma or irregularities at its margins<sup>106,112</sup> 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%.<sup>94</sup> 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.<sup>95</sup> 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.<sup>96</sup>
2. HE occurs early after ICH and is an independent predictor of ND, mortality, and poor functional outcome.<sup>30,111</sup> 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.<sup>97</sup> 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%).<sup>98</sup> However, delayed IVH has been reported in 21% of patients with no initial IVH, and infrequently beyond 24 hours,<sup>99</sup> 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.<sup>113,114</sup> 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,<sup>100,115</sup> whereas other evidence indicated that routine serial neuroimaging may have some value in patients with moderate or severe TBI.<sup>101</sup> 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,<sup>102</sup> 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

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.<sup>104</sup> Mortality and poor modified Rankin Scale (mRS) score at 90 days were greater in patients with CTA-positive spot sign. Subsequent meta-analyses<sup>106–108</sup> 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).<sup>103</sup> 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.<sup>105</sup> 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,<sup>116</sup> this risk remains a relevant consideration in obtaining this study.

- 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<sup>112</sup> (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.<sup>106</sup>

### 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. <sup>117,118</sup>
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. <sup>119</sup>
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. <sup>117,118,120–122</sup>
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. <sup>117,118,120–122</sup>
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). <sup>118,123,124</sup>
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. <sup>118</sup>
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. <sup>125</sup>

### Synopsis

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

lead to acute brain parenchymal bleeding.<sup>126</sup> 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.<sup>118</sup> However, there is substantial heterogeneity in clinical practice in how, when, and in whom an underlying macrovascular cause is explored.<sup>127</sup> 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.<sup>128</sup> 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.<sup>117,118,120,129,130</sup> CT or magnetic resonance venography should be included with CTA or MRA when clinical factors or ICH location suggests possible cerebral venous thrombosis.<sup>131</sup> 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 anti-hypertensive drugs before ICH, or evidence of left ventricular hypertrophy on admission ECG. None of the 291 patients had complications with CTA.<sup>118</sup> 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.<sup>118</sup> 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.<sup>117</sup>

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).<sup>119</sup> 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.<sup>119</sup>
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.<sup>129,132</sup> 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.<sup>120,129</sup>
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%.<sup>118</sup> In addition to the DIAGRAM score,<sup>117</sup> the simple ICH score<sup>121</sup> and secondary ICH score<sup>120,129</sup> 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.<sup>122</sup> Female sex was identified as a predictor of higher likelihood of a macrovascular

lesion in the secondary ICH derivation study<sup>120</sup> but not in validation studies.<sup>129,133</sup>

5. MRI and MRA may provide valuable information on DSA-negative ICH causes (such as CAA, deep perforating vasculopathy, cavernous malformation, or malignancy).<sup>123,124</sup> 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%.<sup>118</sup> Both CTA and MRA appear to have good sensitivity and specificity after ICH for the detection of intracranial vascular malformations.<sup>128</sup> 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<sup>134</sup> 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.<sup>118,135</sup> 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.<sup>125</sup>

### 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  $\beta$ -amyloid.<sup>136,137</sup>
- 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. <sup>138</sup>
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. <sup>139,140</sup>



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 mmHg, acute lowering of SBP to a target of 140 mmHg with the goal of maintaining in the range of 130 to 150 mmHg is safe and may be reasonable for improving functional outcomes. <sup>138,141–147</sup>
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. <sup>148</sup>
3: Harm	B-R	5. In patients with spontaneous ICH of mild to moderate severity presenting with SBP >150 mmHg, acute lowering of SBP to <130 mmHg is potentially harmful. <sup>146,149,150</sup>

### Synopsis

Most patients with acute ICH present with elevated BP. Elevated BP on presentation is associated with greater HE, ND, death, and dependency.<sup>151–153</sup> Therefore, it is intuitive to treat high BP during the acute phase of ICH. However, results from randomized clinical trials have been equivocal.<sup>141,146</sup> 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,<sup>141,146</sup> meta-analyses,<sup>138,142,144,145,147</sup> and several post hoc analyses of the INTERACT2 and ATACH-2 trials.<sup>139,154,155</sup> As a primary recommendation, lowering systolic BP (SBP) to a target range of 130 to 140 mmHg 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 mmHg. 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 mmHg in patients presenting with ICH and elevated BP is potentially harmful and should be avoided.

### Recommendation-Specific Supportive Text

- Several studies have shown that high SBP variability during the hyperacute and acute phases of ICH is associated with poor outcomes.<sup>138,154,156</sup> 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.<sup>154</sup> 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.<sup>138</sup> 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.<sup>157</sup>

- 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.<sup>141,146</sup> 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.<sup>139</sup> In INTERACT2, reductions in SBP ≥20 mmHg during the first hour after randomization and maintained for 7 days were associated with lowest risks of death and major disability.<sup>140</sup> 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.
- EIBPL in patients with mild to moderate ICH (GCS score ≥5, excluding massive ICH) and SBP >150 to 220 mmHg to 140 mmHg appears to be safe. In INTERACT2, EIBPL to a target of 140 mmHg with cessation of treatment at SBP <130 mmHg 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.<sup>141</sup> The mean minimum SBP in the EIBPL group was 150 mmHg. In ATACH-2, EIBPL to a target of 110 to 139 mmHg was not associated with a lower rate of death or disability compared with standard reduction to 140 to 179 mmHg.<sup>146</sup> 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 mmHg.<sup>143</sup> Several meta-analyses indicated that EIBPL is safe overall and not associated with increased risk for SAEs, severe hypotension, ND, or mortality.<sup>138,142,144,145,147</sup> 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.<sup>158</sup>

Significant heterogeneity by BP-lowering strategy and agent was a limitation. Although patients with SBP >220 mmHg 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  $\geq$ 10, ICH volume  $\geq$ 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.<sup>148</sup> 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 mmHg was associated with increased mortality and poor functional outcomes, respectively, suggesting that BP reduction be accompanied by maintenance of CPP of 60 to  $\geq$ 70 mmHg in patients with large ICH, ICP elevation, or compromised CPP.<sup>159,160</sup>
5. Compared with INTERACT2, ATACH-2, which did not exclude patients with initial SBP >220 mmHg, did not show added benefit by lowering SBP to 110 to 139 mmHg. Although the SBP target of 110 to 139 mmHg did not worsen neurological outcomes or increase mortality, the additional SBP reduction was associated with increased renal and SAEs during the follow-up period.<sup>141,146</sup> The mean minimum SBP for the EIBPL group in INTERACT2 was 150 mmHg compared with 129 mmHg in ATACH-2, implying that EIBPL to <130 mmHg may negate potential benefits. This is consistent with a secondary analysis of INTERACT2<sup>149</sup> that showed that an achieved mean SBP <130 mmHg was associated with a modest increase in physical dysfunction and that SBP of 130 to 139 mmHg 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  $\geq$ 25 mL, and higher doses of nicardipine were associated with increased risk for acute renal injury.<sup>155</sup> A post hoc analysis of ATACH-2 in participants with initial SBP  $\geq$ 220 mmHg (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.<sup>150</sup> Similarly, a prospective single-center cohort study of 448 patients with ICH determined that a threshold maximum SBP reduction of 90

mmHg was significantly associated with acute kidney injury regardless of preexisting chronic kidney disease.<sup>161</sup> 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 mmHg 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,  $\approx$ 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  $\geq$ 120 mmHg, 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

suggest that large SBP reductions >20 mmHg 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 mmHg in the first hour and between 40 and 60 mmHg, respectively (compared with <20 mmHg), 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 non-invasive 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.

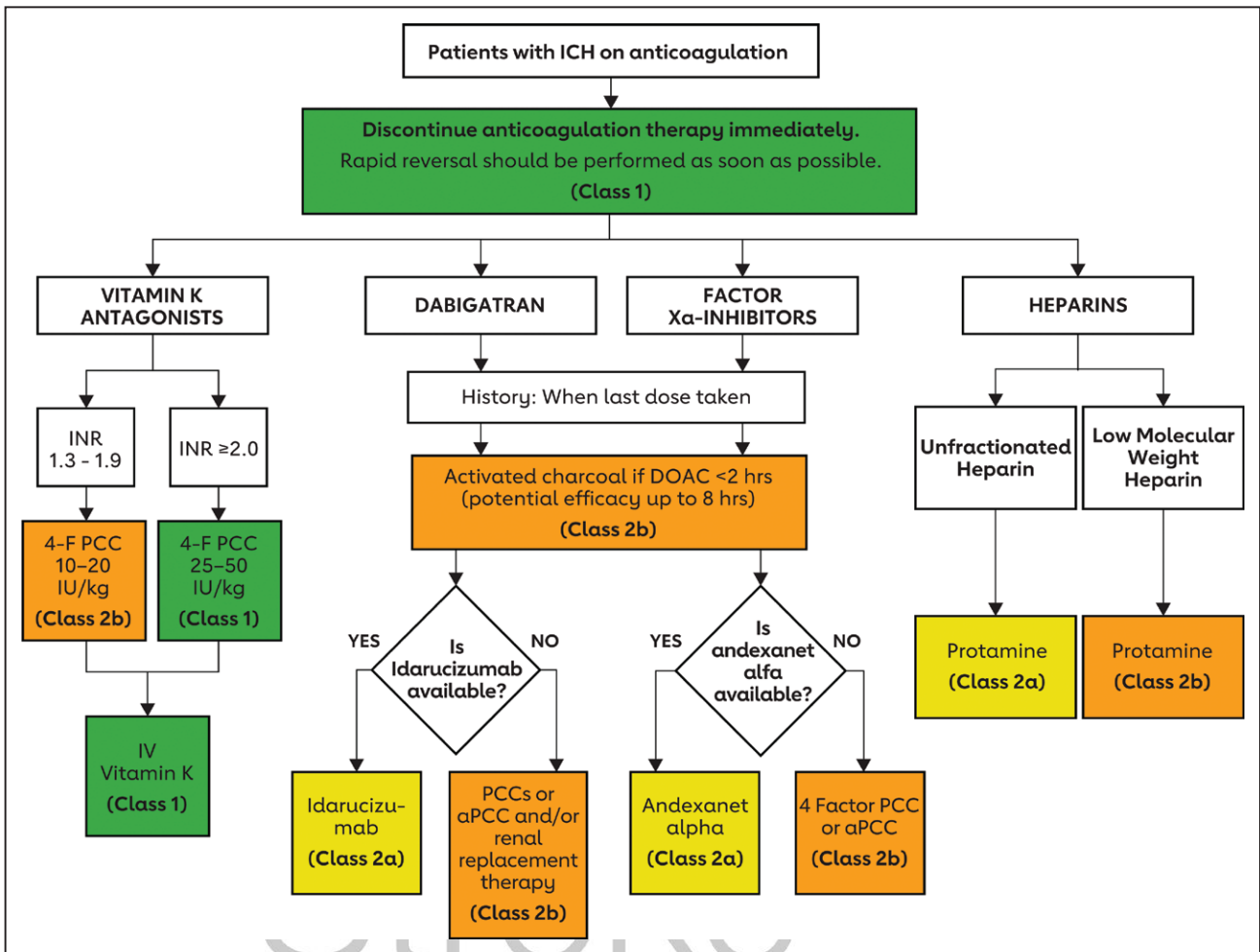
COR	LOE	Recommendations
<b>1</b>	<b>C-LD</b>	1. In patients with anticoagulant-associated spontaneous ICH, anticoagulation should be discontinued immediately and rapid reversal of anticoagulation should be performed as soon as possible after diagnosis of spontaneous ICH to improve survival. <sup>162</sup>
VKAs		
<b>1</b>	<b>B-R</b>	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. <sup>163</sup>
<b>1</b>	<b>C-LD</b>	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. <sup>164,165</sup>
<b>2b</b>	<b>C-LD</b>	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. <sup>162,164</sup>
DOACs		
<b>2a</b>	<b>B-NR</b>	5. In patients with direct factor Xa inhibitor-associated spontaneous ICH, andexanet alfa is reasonable to reverse the anticoagulant effect of factor Xa inhibitors. <sup>166,167</sup>
<b>2a</b>	<b>B-NR</b>	6. In patients with dabigatran-associated spontaneous ICH, idarucizumab is reasonable to reverse the anticoagulant effect of dabigatran. <sup>168</sup>

Recommendations for Anticoagulant-Related Hemorrhage (Continued)		
COR	LOE	Recommendations
<b>2b</b>	<b>B-NR</b>	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. <sup>169-171</sup>
<b>2b</b>	<b>C-LD</b>	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. <sup>172-174</sup>
<b>2b</b>	<b>C-LD</b>	9. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, aPCC or PCCs may be considered to improve hemostasis. <sup>175,176</sup>
<b>2b</b>	<b>C-LD</b>	10. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, renal replacement therapy (RRT) may be considered to reduce dabigatran concentration. <sup>177</sup>
Heparins		
<b>2a</b>	<b>C-LD</b>	11. In patients with unfractionated heparin (UFH)-associated spontaneous ICH, intravenous protamine is reasonable to reverse the anticoagulant effect of heparin. <sup>178</sup>
<b>2b</b>	<b>C-LD</b>	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. <sup>178</sup>

### 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<sup>163</sup> 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<sup>168</sup> and andexanet alfa,<sup>166</sup> 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<sup>176</sup>



**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.<sup>169–171</sup> RRT may reduce dabigatran concentration.<sup>177</sup> In patients on heparin, protamine reverses the anticoagulant effect.<sup>178</sup>

### 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).<sup>162</sup> 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.<sup>179</sup>

- 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.<sup>180</sup> 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.<sup>181,182</sup>
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).<sup>163</sup> In addition, 4-F PCC was associated with a reduction in HE (18.3% versus



- 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  $\geq 2.0$  included 24 patients with intracranial hemorrhage.<sup>183</sup> 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.<sup>87</sup> 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.<sup>87</sup>
- In a case review of 17 patients with VKA-associated major bleeding, PCC rapidly corrected the INR when given with or without vitamin K.<sup>165</sup> 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),<sup>163</sup> 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.<sup>164</sup>
  - 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.<sup>164</sup> A case review of 88 patients with warfarin-related ICH and INR  $> 1.2$  demonstrated survival benefit of PCC over FFP.<sup>162</sup> Dosing information for 4-F PCC recommends doses for use only when INR  $\geq 2.0$ . An observational study of 205 patients with VKA-related ICH treated with PCC to an INR  $\geq 1.5$  noted increased risk of venous thromboembolism (VTE) with higher doses of PCC ( $> 2000$  and  $3000$  IU).<sup>184</sup> Hence, a lower dose of 10 to 20 IU/kg is suggested when INR is  $< 2.0$  but  $\geq 1.3$  to achieve rapid correction of INR and limit HE.
  - 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.<sup>166</sup> 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.<sup>167</sup> 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.<sup>185</sup> 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.<sup>186</sup> In another small comparison, andexanet alfa was similar to PCC in terms of stability of hematoma on CT at 6 and 24 hours.<sup>187</sup> 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.<sup>188</sup> The recommended dosing of andexanet alfa depends on the specific factor Xa inhibitor and the time since last dose.<sup>189</sup>
  - 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.<sup>168,190</sup> 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<sup>191</sup> and Europe<sup>175,192,193</sup> have shown similar rates of

- 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.<sup>194–198</sup> 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.<sup>171</sup> 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.<sup>170</sup> 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.<sup>169</sup> 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.<sup>199</sup> 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.<sup>173</sup> 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.<sup>174</sup> Similarly, activated charcoal given to healthy volunteers up to 8 hours after ingestion of rivaroxaban significantly reduced exposure.<sup>172</sup> 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.<sup>176</sup> 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.<sup>175</sup> 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.<sup>200</sup> 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.<sup>201,202</sup>
  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 in 1 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.<sup>177</sup>
  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.<sup>178</sup> 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.<sup>203</sup> Intravenous protamine should not exceed 50 mg/10 min because of the risk of hypotension and bronchoconstriction; repeated smaller doses are preferable.<sup>178</sup>
  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.<sup>204</sup> Therefore, intravenous protamine is reasonable to partially reverse the anticoagulant effect of LMWH.<sup>178</sup> Andexanet alfa has also been shown to significantly reduce anti-factor Xa levels in 16 patients taking enoxaparin.<sup>166</sup>

### 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.<sup>205</sup> 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. <sup>206</sup>
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. <sup>207-209</sup>
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. <sup>210</sup>

#### 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.<sup>211</sup> 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.<sup>212</sup> In an RCT, the subset of patients with antiplatelet therapy had more unfavorable functional outcome and higher mortality.<sup>213</sup> 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,<sup>214-216</sup> whereas for spontaneous ICH in patients being treated with antiplatelet agents, no convincing benefit has been demonstrated.<sup>207-210,213</sup> 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.<sup>206</sup>

#### 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.<sup>206</sup> 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,<sup>207,209</sup> treatment with desmopressin (0.3 µg/kg) was associated with reduced expansion of the hematoma in 1 of the studies.<sup>207</sup> The latter study

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.<sup>208</sup>

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.<sup>210</sup> 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 P2Y<sub>12</sub> 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.<sup>217</sup> 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. <sup>218,219</sup>
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. <sup>220-222</sup>

#### Synopsis

HE occurs in up to a third of patients after ICH and is associated with poor outcome.<sup>103</sup> 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.<sup>223-226</sup> 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.<sup>219</sup> 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.<sup>218</sup> Meta-analysis of recombinant factor VIIa RCTs showed no benefit on HE, functional outcome, or SAEs.<sup>227</sup> 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,<sup>228</sup> 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



there was no difference in expansion or functional outcome between the treatment groups.<sup>229</sup>

- 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.<sup>222</sup> 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.<sup>220,221</sup> 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.<sup>230</sup>

### 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. <sup>231,232</sup>

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. <sup>233</sup>
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. <sup>233,234</sup>
1	C-LD	4. In patients with spontaneous ICH, care delivery that includes multidisciplinary teams trained in neurological assessment is recommended to improve outcomes. <sup>99,235,236</sup>
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. <sup>231,237,238</sup>
2a	B-NR	7. In patients with moderate to severe spontaneous ICH, IVH, hydrocephalus, or intratentorial location, provision of care in a neuro-specific ICU compared with a general ICU is reasonable to improve outcomes and reduce mortality. <sup>235,239–241</sup>
2b	B-NR	8. In patients with IVH or intratentorial ICH location, transfer to centers with neurosurgical capabilities might be reasonable to improve outcomes. <sup>102,233,234</sup>
2b	C-LD	9. In patients with larger supratentorial ICH, transfer to centers with neurosurgical capabilities may be reasonable to improve outcomes. <sup>233,234</sup>

### Synopsis

Patients with ICH who have clinical hydrocephalus, IVH, or intratentorial 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

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.<sup>242,243</sup> 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.<sup>231,232</sup>
2. In patients with ICH, initiating coagulopathy reversal and BP control before transfer is recommended to avoid delays in treatment.<sup>233</sup> 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.<sup>233</sup>
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.<sup>244</sup> 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.<sup>233,234</sup>
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.<sup>231,235,236</sup> The highest-risk period for neurological decline is within the first 12 hours after the hemorrhage, with deterioration events becoming uncommon after 48 hours.<sup>245,246</sup> 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.<sup>99,102</sup>
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  $\leq 8$ ) 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.<sup>247</sup> 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 10811 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.<sup>237</sup> 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.<sup>238,248</sup> A

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]).<sup>238</sup> 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.<sup>231</sup> 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.<sup>249–251</sup> Criteria include low ICH volume (<20 mL), low NIHSS score ( $\leq 10$ ), high GCS score ( $\geq 13$ ), 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  $\geq 30$  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.<sup>235,236,239–241,252,253</sup> 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.<sup>235,240</sup> In 1 study, having a full-time intensivist was associated with a lower mortality rate.<sup>239</sup>
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.<sup>102,233,234,254</sup> 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.<sup>233</sup>
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.<sup>102,233,234,255</sup> Patients with moderate to severe supratentorial ICH (identified in most studies by volume  $\geq 30$  mL or GCS score  $< 8$ ) may benefit from neurosurgical evaluation.<sup>233,234,254</sup>

### 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. <sup>256–259</sup>
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. <sup>256,260–265</sup>
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. <sup>266–268</sup>
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. <sup>269–273</sup>

## 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.<sup>258</sup> 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,<sup>256</sup> with sustained benefits on long-term survival at 4 years (>20%) compared with the control units.<sup>258</sup> 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.<sup>257</sup> 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.<sup>259</sup>
2. The risk of death resulting from pneumonia for patients with stroke is ≈35%.<sup>262</sup> 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.<sup>256</sup> 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.<sup>264</sup> Patients with a positive dysphagia screen have a significantly higher 5-year mortality rate,<sup>261</sup> 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).<sup>262</sup> 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<sup>265</sup> 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.<sup>260,263</sup> 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<sup>266</sup> 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.<sup>266</sup> 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.<sup>267</sup> 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 continuous cardiac monitoring on arrival.
4. Infectious complications are associated with poor long-term outcomes, including readmission within the first 30 days after ICH.<sup>272,273</sup> A study found that patients with IVH ( $P<0.001$ ) and patients with ICH scores >2 also had higher risk of infectious complications ( $P=0.0014$ ).<sup>271</sup> ICH score >2 was found to be a significant risk factor for infectious complications (OR, 1.7 [95% CI, 1.2–2.3];  $P=0.02$ ).<sup>269</sup> 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.



### 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.<sup>274</sup>

### 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. <sup>275,276</sup>
2a	C-LD	2. In nonambulatory patients with spontaneous ICH, low-dose UFH or LMWH can be useful to reduce the risk for PE. <sup>277-280</sup>
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. <sup>277,281,282</sup>
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. <sup>276,278,283,284</sup>
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. <sup>285</sup>
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. <sup>286,287</sup>

### 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<sup>283</sup> and network meta-analysis of 4 RCTs.<sup>276</sup> A meta-analysis of 4 studies demonstrated that heparin or LMWH reduces the risk of PE<sup>278</sup> when initiated 48 to 96 hours after onset of the hemorrhage or the diagnosis without a significant increase in hematoma enlargement.<sup>277,279,281,282</sup> Graduated compression stockings of any length are not effective against symptomatic DVT according to 2 large RCTs and 2 meta-analyses.<sup>276,278,283,284</sup> 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.<sup>285</sup> 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.<sup>286,287</sup>

### Recommendation-Specific Supportive Text

1. The in-hospital incidence of thromboembolic complications in patients with ICH is ≈7%,<sup>288</sup> and the risk of DVT is 4 times higher than in patients with acute ischemic stroke,<sup>289</sup> 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.<sup>276</sup> 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%).<sup>275</sup> 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.<sup>275</sup>
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.<sup>278</sup> 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<sup>277</sup> and was

- not reported in another study.<sup>280</sup> 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.<sup>279</sup> Only 1 of the 9 studies had a low probability of bias.
- 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<sup>277</sup> and 2 larger retrospective studies<sup>281,282</sup> 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,<sup>277</sup> 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),<sup>281</sup> and within 48 hours from symptom onset in the smaller retrospective study.<sup>282</sup> 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.<sup>282</sup> 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%.<sup>290</sup>
  - 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.<sup>278</sup> 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.<sup>283</sup> 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.<sup>284</sup> 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.<sup>276</sup> The design of all the studies included screening with compression ultrasound for DVT, thereby also including asymptomatic events in the efficacy outcome.
  - 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.<sup>285</sup> 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.
  - 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  $\geq 4$  at discharge and at follow-up after 3 months.<sup>291</sup> 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.<sup>286</sup> 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.<sup>287</sup> 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.

- 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. <sup>61,292–294</sup>
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. <sup>99,245,292,294</sup>
2a	C-LD	3. In patients with spontaneous ICH, specialized nurse stroke competencies can be effective in improving outcome and mortality. <sup>295–297</sup>

#### 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,<sup>61</sup> whereas as many as 70% had ND in the first 24 hours of admission.<sup>292</sup> Specialized nurse competency training programs are associated with increased nursing satisfaction and have been shown to improve compliance with stroke evidence-based protocols.<sup>296</sup>

#### 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 ultra-early neurological decline compared with patients with ischemic stroke (30.8% versus 6.1%).<sup>293</sup> 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.<sup>102</sup> 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.<sup>102,292</sup> 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.<sup>245</sup> 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

of ICU delirium and sleep deprivation, which may have further negative impact on patient functional outcome, cognition, and quality of life.<sup>246,298</sup> 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.<sup>295</sup> 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.<sup>296</sup> 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. <sup>256,299</sup>
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. <sup>299–301</sup>
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. <sup>78,302–307</sup>

### 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.<sup>256</sup> Hyperglycemia on presentation may herald a worse prognosis.<sup>308,309</sup> However, tight glucose control may increase the risk of hypoglycemic events and worsen outcomes.<sup>299–301</sup> The ideal evidence-based approach to glucose management in patients with ICH has remained elusive.<sup>310</sup>

### 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.<sup>256,299</sup> 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.<sup>256</sup>
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.<sup>299–301,309</sup> The NICE-SUGAR trial (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation)



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.<sup>299</sup> An important finding was that severe hypoglycemic events (glucose  $\leq$ 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.<sup>300</sup> 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.

- 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.<sup>78,302–307</sup> 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.<sup>299</sup> 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 43 and 44.		
COR	LOE	Recommendations
2b	C-LD	1. In patients with spontaneous ICH, pharmacologically treating an elevated temperature may be reasonable to improve functional outcomes. <sup>311–313</sup>
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. <sup>314–317</sup>

### 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.<sup>318–321</sup> Fever appears to be associated with both higher clinical severity and worse outcomes<sup>322</sup>; however, evidence for whether treating fever improves outcomes is conflicting.<sup>311,313</sup> 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.<sup>323</sup>

### Recommendation-Specific Supportive Text

- Fever in patients with ICH has been associated with worse outcomes.<sup>318,321</sup> Treating fever seems reasonable; however, there is less evidence that therapeutic temperature modulation improves outcomes.<sup>315,316,320</sup> 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.<sup>320</sup> 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.<sup>312</sup> 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

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.<sup>313</sup> In a prospective database, pharmacological treatment of temperatures  $\geq 37.5^\circ\text{C}$  for 48 hours was associated with an increased likelihood of a good outcome at 3 months.<sup>311</sup> 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.<sup>312</sup> 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.

- 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 perihematoma volume.<sup>314–316</sup> However, therapeutic hypothermia is not without risk and should be considered of unclear benefit.<sup>315–317,324</sup>

### 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.
- Perihematoma 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. <sup>325,326</sup>
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 ( $\geq 24$ hours) is reasonable to diagnose electrographic seizures and epileptiform discharges. <sup>327</sup>
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. <sup>328–331</sup>

### 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,”<sup>332</sup> and, in the context of an electrographic seizure, the definition outlined by the American Clinical Neurophysiology Society, “epileptiform discharges averaging  $>2.5$  Hz for  $\geq 10$  s ( $>25$  discharges in 10 s) or any pattern with definite evolution and lasting  $\geq 10$  s.”<sup>332a</sup> 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.<sup>327,333–335</sup> 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.<sup>327</sup> 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.<sup>325,329,330</sup> Another consideration is that seizures may be a marker of ICH rather than specifically affecting outcomes.<sup>327</sup>

### Recommendation-Specific Supportive Text

- There is uncertainty about the prognostic significance of abnormal electrographic patterns in the setting of ICH.<sup>325,326</sup> The clinical context should

therefore be considered in the decision-making process. The recommendation is to initiate anti-epileptic 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).<sup>325</sup> 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.<sup>336</sup> Other studies similarly failed to demonstrate a clear mortality benefit from treating seizures in the context of ICH.<sup>337–339</sup> Still others showed better outcomes in patients with post-ICH seizures.<sup>333,334</sup> 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<sup>340</sup> 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.<sup>327</sup>
4. Earlier studies suggested that prophylactic anti-seizure drugs such as phenytoin were associated with worse outcomes in patients with ICH.<sup>335,341</sup> Consequently, the use of alternative prophylactic antiseizure drugs such as levetiracetam may have become more common.<sup>342</sup> 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,<sup>328–331,343</sup> but specific domains of abilities such as cognitive function might be negatively affected.<sup>344</sup> 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.<sup>345</sup> 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.<sup>346</sup>

### 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 48 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. <sup>347–350</sup>
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. <sup>159,351–356</sup>
2b	B-NR	3. In patients with spontaneous ICH, the efficacy of early prophylactic hyperosmolar therapy for improving outcomes is not well established. <sup>357–361</sup>
2b	C-LD	4. In patients with spontaneous ICH, bolus hyperosmolar therapy may be considered for transiently reducing ICP. <sup>362–364</sup>
3: No Benefit	B-R	5. In patients with spontaneous ICH, corticosteroids should not be administered for treatment of elevated ICP. <sup>365–369</sup>

## 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  $\leq 8$ , 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.<sup>370</sup> EVD is a lifesaving procedure that can rapidly decrease ICP secondary to hydrocephalus.<sup>350</sup> 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.<sup>347</sup> 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.<sup>348</sup> A systematic review demonstrates that treatment with ventricular drainage, combined with fibrinolytics, may improve outcome in patients with ICH with intraventricular extension.<sup>349</sup> 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.<sup>371</sup> In a retrospective review of primary ICH affecting the thalamus, EVD placement showed no significant correlation with clinical outcomes.<sup>372</sup> 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.<sup>373</sup>
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.<sup>374</sup> However, an analysis of 2 RCTs suggests that ICP is infrequently elevated during EVD monitoring and drainage in patients with severe IVH.<sup>159,356</sup> A 2019 systematic review and meta-analysis indicates that the prevalence and mortality of intracranial hypertension are high after ICH.<sup>352</sup> 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.<sup>159,354–356,370</sup> 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.<sup>353</sup> 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,<sup>35</sup> although long-term mortality in MISTIE III was significantly associated with higher proportion of time with high ICP and low CPP in monitored patients.<sup>160</sup> 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.<sup>376,377</sup> The studies focused on prophylactic use of mannitol infusion have not demonstrated clinical benefit,<sup>357,360,361</sup> 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.<sup>359</sup> 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.<sup>357</sup> 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.<sup>360</sup> Although the efficacy of hyperosmolar treatments to attain serum hyperosmolarity is not well established, usual supportive



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.<sup>378</sup> 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.<sup>362</sup> 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.<sup>363</sup> 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.<sup>363</sup> 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.<sup>364</sup>
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.<sup>368</sup> A second RCT performed in 1989 demonstrates no differences in outcomes in patients with ICH treated with corticosteroids versus those treated without corticosteroids.<sup>365</sup> A 1998 RCT suggests that dexamethasone does not likely cause an unacceptably high rate of complications but also does not provide a benefit.<sup>366</sup> More recently, a Cochrane review<sup>367</sup> and a meta-analysis<sup>369</sup> 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 mmHg and a CPP of 50 to 70 mmHg, 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 S5 and S6.

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. <sup>379–388</sup>
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. <sup>382,383,385–387,389,390</sup>
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. <sup>379–385,387,388</sup>

## 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.<sup>379–388,391,392</sup> The present guideline uses primarily data from the largest RCT of MIS (MISTIE III),<sup>381</sup> meta-analyses of trials comparing MIS with conventional craniotomy and standard medical care,<sup>379,380,382–390,393–395</sup> and smaller RCTs.<sup>391,392,396–412</sup> 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).<sup>381</sup> Although smaller, likely underpowered RCTs did not always show a mortality benefit for MIS,<sup>392,400,401,406,408</sup> 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.<sup>380,382,386–390,394</sup> 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.<sup>381</sup> 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.<sup>391,398,400,405,406,408,411–413</sup> 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.<sup>393</sup>

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<sup>389,398,399,411,412,414</sup> 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.<sup>383,385–387,389,390,394,395</sup> A network meta-analysis suggested the highest ranking of favorable prognosis for stereotactic aspiration, followed by endoscopy, then craniotomy, and last standard medical care.<sup>382</sup> 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.<sup>399</sup>
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.<sup>391,392,396–399,401,403,408,412,413</sup> 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.<sup>381</sup> 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.<sup>379,380,382–390,394</sup> 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,<sup>387</sup> whereas MISTIE III and 2 other meta-analyses found that hematoma volume did not modify the effect of surgery.<sup>379,381,384</sup>

## Knowledge Gaps and Future Research

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

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 intrahematoma 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. <sup>347-349</sup>
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. <sup>415-418</sup>
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. <sup>382,407,415-419</sup>

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. <sup>347-349</sup>
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. <sup>419,420</sup>

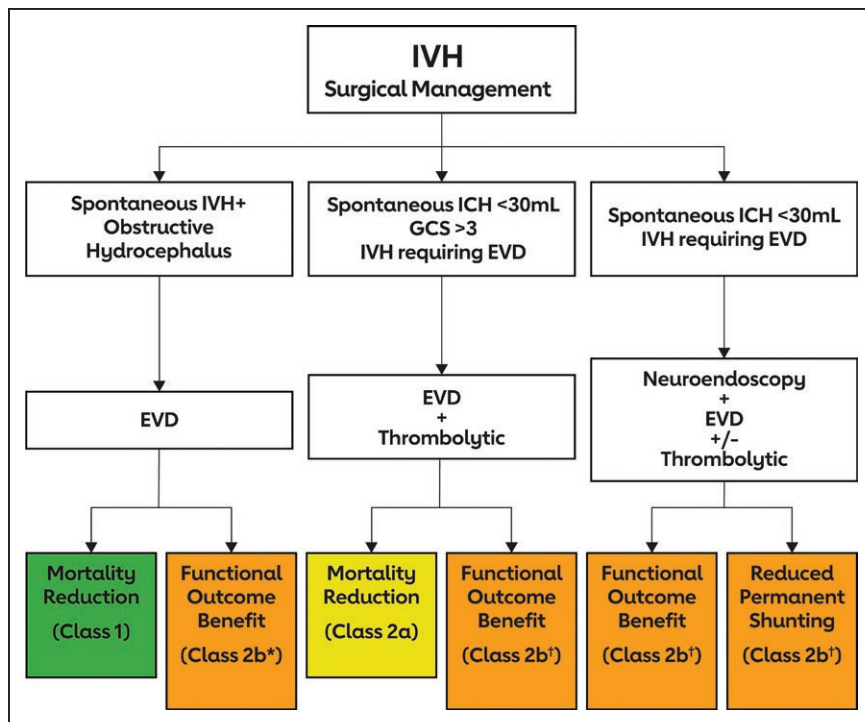
**Synopsis**

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.<sup>421</sup> IVH predicts a worse prognosis secondary to increased IVH volume and blood breakdown products that promote inflammatory meningitis and hydrocephalus.<sup>126</sup> Insertion of an EVD to treat intracranial hypertension and remove blood products improves survival.<sup>347-349</sup> The addition of thrombolytic irrigation with alteplase or urokinase hastens intraventricular clot removal and results in further mortality reduction.<sup>416,422</sup> 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]),<sup>416</sup> systematic reviews or meta-analyses of trials comparing (1) EVD with and without IVT with conservative treatment<sup>349</sup> and (2) IVT with either EVD plus saline or EVD alone,<sup>415,417,418</sup> and several smaller RCTs.<sup>356,423-425</sup> 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<sup>348</sup>]), EVD placement alone is associated with improved survival compared with conservative treatment.<sup>347-349</sup> 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.<sup>348</sup> A smaller retrospective analysis found a positive association of EVD alone with survival at hospital discharge in patients presenting with

Downloaded from http://ahajournals.org by on June 1, 2022



**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.<sup>347</sup> There were no age limits on these studies.

- 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.<sup>416</sup> Smaller RCTs also have shown a mortality benefit for IVT,<sup>356,423–425</sup> 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.<sup>415,417,418</sup> 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.<sup>416</sup> 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.
- 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.<sup>416</sup> 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.<sup>415,417,419,426</sup> 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.

- Compared with conservative treatment, there is uncertainty over whether EVD alone improves functional outcomes. In a systematic review of studies



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.<sup>349</sup> In a large retrospective analysis with propensity score matching, EVD use was not associated with functional outcome at discharge.<sup>348</sup> 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.<sup>347</sup> However, retrospective studies are unable to evaluate unmeasured confounders that contribute to the decision to place EVDs in patients with IVH.

- Endoscopic surgery for hypertensive IVH combined with EVD with or without IVT has been studied in small RCTs and observational studies.<sup>419,420,427,428</sup> 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.<sup>427,428</sup> 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.<sup>420</sup> 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.<sup>419</sup> 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  $\leq 2$ ) 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. <sup>380,382,384,393,429-431</sup>
2b	C-LD	2. In patients with supratentorial ICH who are deteriorating, craniotomy for hematoma evacuation might be considered as a lifesaving measure. <sup>382,384,429,432</sup>

### Synopsis

For most patients, craniotomy for spontaneous ICH remains of uncertain benefit compared with medical management alone.<sup>429,431</sup> RCT results have been inconclusive. Early data were mixed,<sup>393,433-440</sup> with 2 large RCTs finding no benefit in functional outcome or mortality.<sup>429,431</sup> 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.<sup>432</sup> 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,<sup>436</sup> 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

performed primarily >12 hours after onset.<sup>441</sup> Two smaller single-center RCTs requiring surgery within ≤12 hours of onset have suggested benefit.<sup>430,437</sup> 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.<sup>429,431</sup> A patient-level data meta-analysis performed contemporaneously suggested that certain cohorts might benefit,<sup>393</sup> and a smaller (n=108) single-center RCT found that craniotomy improved functional outcome.<sup>430</sup> Three meta-analyses published in 2020 provide mixed results: 2 meta-analyses suggest a benefit in functional outcome and mortality with any surgery,<sup>382,384</sup> and 1 meta-analysis found no benefit in functional outcome or mortality.<sup>380</sup>
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.<sup>429</sup> 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.<sup>429</sup> This suggestion of a mortality benefit was further supported by a recent small (n=61) RCT that demonstrated improved mortality with surgery<sup>432</sup> and 2 meta-analyses that suggest a possible mortality benefit.<sup>382,384</sup> 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,<sup>437</sup> although not powered for efficacy (n=34), found a promising mortality signal when surgery was performed within 12 hours. More encouragingly, Pantazis et al<sup>430</sup> (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 2.5.

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. <sup>442-444</sup>

### Synopsis

Spontaneous cerebellar hemorrhage is frequently associated with hydrocephalus, brainstem compression, and herniation in the confined space of the posterior fossa.<sup>126</sup> Therefore, hematoma evacuation is often recommended despite a lack of randomized evidence.<sup>414</sup> The present guideline is based primarily on data from a large individual-patient data meta-analysis with propensity score matching,<sup>442</sup> systematic reviews<sup>443,444</sup> and several retrospective studies.<sup>254,445-451</sup> 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.<sup>442</sup> For patients with cerebellar ICH and clinical hydrocephalus, EVD alone is, in theory, potentially harmful, especially if the basal cisterns are compressed.<sup>452</sup> EVD alone may be insufficient when intracranial hypertension impedes blood supply to the brainstem.<sup>445</sup>

### 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.<sup>442</sup> Mortality benefit occurred for patients with larger



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.<sup>443</sup> 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.<sup>444</sup> 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.<sup>450</sup> One retrospective study reported trends for improved mortality and functional outcome for suboccipital decompression and hematoma evacuation compared with evacuation alone.<sup>448</sup> 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.<sup>442,445–448,450,451</sup>

### Knowledge Gaps and Future Research

- A perceived lack of equipoise concerning the life-saving 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 S6 through S8.

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. <sup>453–460</sup>
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. <sup>458–462</sup>

### 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,<sup>458,462</sup> retrospective series,<sup>453–457,461,463–471</sup> a systematic review,<sup>459</sup> and a meta-analysis.<sup>460</sup> 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.<sup>461</sup> 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.<sup>454,458,462,463,465,466,468,471</sup> Many include patients within 24 hours of hemorrhage. Overall, the studies suggest that surgery may improve mortality compared with medical

management.<sup>453–457,470</sup> Both a meta-analysis and a systematic review suggest that decompressive craniectomy may offer mortality benefits in the setting of supratentorial ICH.<sup>459,460</sup> 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%.<sup>459</sup>

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.<sup>462</sup> 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.<sup>458</sup> 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.<sup>458</sup> Retrospective case series that compare decompressive craniectomy and craniotomy with hematoma evacuation present conflicting results (some favor decompressive craniectomy, others favor hematoma evacuation).<sup>463–469</sup> A single retrospective study compared decompressive craniectomy with and without associated hematoma evacuation. Performance of hematoma evacuation did not change functional outcomes.<sup>461</sup> 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.<sup>460</sup> The systematic review reported a pooled favorable outcome in 53%.<sup>459</sup>

### 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 59.

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. <sup>472–474</sup>
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. <sup>472,473</sup>
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. <sup>475,476</sup>

### 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



score, although modifications of the original ICH score<sup>472,473</sup> and other scores also have been developed.<sup>474</sup> 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.<sup>477,478</sup> 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.

- Several recent systematic meta-analyses have quantified the validity of the ICH score for prediction of mortality and functional outcome.<sup>472,473</sup> 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.
- 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,<sup>476</sup> 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.<sup>475</sup>

### 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 20.		
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. <sup>479-484</sup>
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. <sup>485</sup>
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. <sup>180,479,486,487</sup>

### 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.<sup>479,484,488</sup> Therefore, recommendations are made about the use and intent of these care

limitations and the process of shared decision-making between surrogates and physicians. Issues considered in this section intersect with outcome prediction and prognostication<sup>476,489</sup> (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.<sup>479,480,484</sup> 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.<sup>481</sup> DNAR orders also may be used differently in various cultures.<sup>483</sup> Furthermore, physicians should ensure careful assessment of reversible confounders such as sedation, hydrocephalus, and delirium in considering institution of treatment limitations.<sup>482</sup> 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.<sup>485</sup> 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.<sup>180,479,486,487</sup> 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

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. <sup>231,232</sup>
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. <sup>490</sup>
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. <sup>491,492</sup>
3: No Benefit	A	4. In patients with spontaneous ICH without depression, fluoxetine therapy is not effective to enhance poststroke functional status. <sup>493-497</sup>
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. <sup>498,499</sup>

#### 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<sup>500</sup> 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.<sup>232</sup>
2. Many patients with mild to moderate disability (eg, mRS score  $\leq 3$ ) after ICH can benefit from early supported discharge.<sup>490</sup> 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,<sup>501</sup> Canada,<sup>502</sup> Australia,<sup>503</sup> Norway,<sup>504</sup> Thailand,<sup>505</sup> Northern Ireland<sup>506</sup>).
3. Studies generally support early institution of rehabilitation activities. In a Chinese study<sup>492</sup> 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<sup>491</sup> 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.<sup>495</sup> However, multiple studies of fluoxetine, in either patients with ICH or patients with stroke in general, have not shown beneficial effects on

functional outcome.<sup>493–497</sup> 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.<sup>499</sup> 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.<sup>498</sup>

### 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 mmHg) 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 mmHg.
- 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. <sup>507,508</sup>
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. <sup>509</sup>
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. <sup>510</sup>
2a	B-NR	4. In patients with spontaneous ICH and cognitive impairment, referral for cognitive therapy is reasonable to improve cognitive outcomes. <sup>511–515</sup>
2a	B-NR	5. In patients with spontaneous ICH and pre-existing or new mood disorders requiring pharmacotherapy, continuation or initiation of SSRIs after ICH can be beneficial for the treatment of mood disorders. <sup>508,516–518</sup>
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. <sup>519–521</sup>

### 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,<sup>522</sup> and this persists over time.<sup>523</sup> Thirty-three percent of patients with ICH experience dementia either before or after their ICH,<sup>524</sup> 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.<sup>525</sup> Another study noted 32% prevalence of cognitive impairment at 3 years after stroke.<sup>526</sup> Analysis of neuroimaging features of patients who develop post-ICH dementia suggests underlying CAA as a contributing factor.<sup>525</sup> Neurobehavioral complications after ICH are underrecognized by clinicians, leading to worsened long-term patient-centered outcomes such as independence and community reintegration.<sup>527</sup> Poststroke depression is associated with increased short- and long-term mortality<sup>528–532</sup> and poor functional outcomes<sup>532–534</sup> and leads to greater physical limitations, which can impair rehabilitative efforts.<sup>535</sup>



Poststroke depression also can lead to suicide, which is twice as high in the first 2 years after stroke compared with the general population.<sup>536</sup> Similarly, cognitive impairment predicts poststroke disability<sup>526,535,537</sup> and mortality.<sup>537–539</sup> 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<sup>540,541</sup> and remission of poststroke depression<sup>540,541</sup> in patients who underwent psychotherapy with or without pharmacotherapy. Psychotherapy also significantly reduces poststroke anxiety.<sup>542</sup> Pharmacological therapy is beneficial in reducing poststroke depression and anxiety prevalence and symptoms.<sup>540,542–548</sup> 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.<sup>493,496,549</sup> Several studies suggest that transcranial magnetic stimulation also reduces symptoms of poststroke depression.<sup>544,550</sup>
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.<sup>551</sup> In a meta-analysis, Meader and colleagues<sup>509</sup> 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.<sup>529</sup> 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.<sup>529</sup>

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.<sup>510</sup> 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,<sup>507</sup> but it has a lower specificity for screening.<sup>510,552</sup> 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.<sup>527,553</sup> 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.<sup>554,555</sup> 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.<sup>511,515,556,557</sup> 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,<sup>513</sup> memory deficits,<sup>514</sup> and executive dysfunction.<sup>512</sup> 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

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.<sup>508,558</sup> 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,<sup>508,516,517,559</sup> especially in patients who are taking anticoagulation and strong SSRIs.<sup>508,559,560</sup> This can translate into worsened 3-month neurological outcome.<sup>518</sup> 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.<sup>493,494,496,536,549</sup> 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,<sup>521</sup> 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,<sup>519,520</sup> 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. <sup>562–571</sup>

#### 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.<sup>562,565–571</sup> 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 arteriosclerosis), 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%]).<sup>564</sup> 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.<sup>571</sup> In such scenarios, antithrombotic medications are often contemplated, and the risk of hemorrhage must be weighed against the risk of ischemic

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),<sup>572</sup> the presence of microbleeds<sup>27,573,574</sup> (in particular strictly lobar microbleeds),<sup>27,575</sup> the number of lobar microbleeds (HR, 1.88 for 1 microbleed, 2.93 for 2–4 microbleeds, 4.12 for >4 microbleeds),<sup>572</sup> and the presence of disseminated cortical siderosis (HR, 4.69),<sup>576,577</sup> 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.<sup>578</sup> Recurrence risk also increases with higher measured outpatient BP<sup>563</sup> and age<sup>570,579</sup> (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).<sup>568</sup> Association of ICH recurrence with Hispanic ethnicity has been inconsistent.<sup>568,580</sup>

### 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 73 and 74.		
COR	LOE	Recommendations
1	B-R	1. In patients with spontaneous ICH, BP control is recommended to prevent hemorrhage recurrence. <sup>563,581</sup>
2a	B-NR	2. In patients with spontaneous ICH, it is reasonable to lower BP to an SBP of 130 mmHg and diastolic BP (DBP) of 80 mmHg for long-term management to prevent hemorrhage recurrence. <sup>581,582</sup>

### 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.<sup>93</sup> Despite this, a significant proportion of ICH survivors continue to have poorly controlled BP.<sup>563,583</sup> 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.<sup>581</sup> 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.<sup>563</sup> In PROGRESS (Perindopril Protection Against Recurrent Stroke Study), treatment with perindopril and indapamide reduced mean BP by 10.8/4.4 mmHg 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.<sup>581</sup> 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 mmHg compared with those with SBP of 130 to 139 mmHg (HR, 2.07 [95% CI, 1.22–3.51]), with a nonsignificant trend toward lower rates of ICH with SBP <130 mmHg. Similarly, the risk of ICH was higher in subjects with DBP ≥100 mmHg compared

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

### 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  $\leq$ 120 mmHg 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. <sup>586,587</sup>
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. <sup>588,589</sup>
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. <sup>590–595</sup>
2b	C-LD	4. In patients with AF and spontaneous ICH in whom the decision is made to restart anticoagulation, initiation of anticoagulation $\approx$ 7 to 8 weeks after ICH may be considered after weighing specific patient characteristics to optimize the balance of risks and benefits. <sup>596,597</sup>
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. <sup>598–602</sup>

### 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.<sup>586</sup> 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.<sup>182</sup> 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.<sup>587</sup> 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.<sup>589</sup> 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



(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.<sup>603</sup> 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.<sup>598</sup> 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.<sup>179,590,591,593–595,604</sup> 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.<sup>597</sup> Before 4 to 8 weeks, there appears to be a significant increase in bleeding risk.<sup>596,597</sup> 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.<sup>598,599</sup> 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.<sup>598,599</sup> 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.<sup>601</sup> Other small retrospective studies reported low event rates similar to rates in the patients without ICH<sup>600</sup> and no ischemic stroke or ICH within 30 days of left atrial appendage closure among patients diagnosed with CAA.<sup>602</sup> 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

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 B0 and B1.		
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. <sup>605-609</sup>
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. <sup>610,611</sup>

#### 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).<sup>606,612</sup> 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.<sup>607,609,613-618</sup> 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<sup>610,611</sup>; 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.<sup>612</sup> 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.<sup>606</sup> Additional nonrandomized, observational studies have not found an association with statin use in patients with ICH.<sup>607,609,613,616,618</sup> The risk may be mediated by complex interactions among genetic risk of recurrent ICH, lipid levels, and ICH location.<sup>614,617</sup> In addition, lipophilic statins may be associated with higher rates of ICH than hydrophilic statins.<sup>615</sup> Other retrospective analyses suggest the potential for improved outcomes after ICH with statin use<sup>605,619,620</sup> and a reduction in short- and long-term mortality with statin use.<sup>608,618,621-627</sup> 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.<sup>628-630</sup>

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.<sup>611</sup> A subsequent large meta-analysis found an increased risk of ICH with any NSAID use.<sup>610</sup> 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.<sup>631</sup> 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

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		
Referenced studies that support recommendations are summarized in Data Supplement 52.		
COR	LOE	Recommendations
Lifestyle modification		
2a	C-LD	1. In patients with spontaneous ICH, lifestyle modification is reasonable to reduce BP. <sup>632</sup>
2a	C-LD	2. In patients with spontaneous ICH, avoiding heavy alcohol consumption is reasonable to reduce hypertension and risk of ICH recurrence. <sup>633-635</sup>
2b	C-LD	3. In patients with spontaneous ICH, lifestyle modification, including supervised training and counseling, may be reasonable to improve functional recovery. <sup>636,637</sup>
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. <sup>638</sup>
2a	C-LD	5. In patients with spontaneous ICH, practical support and training for the caregiver are reasonable to improve patients' standing balance. <sup>639</sup>

#### 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.<sup>632,637</sup>

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.<sup>632,640</sup> 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.<sup>641</sup> A meta-analysis<sup>632</sup> 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.<sup>633,634</sup> For those with large alcohol intake, a reduction by half had the strongest impact on BP.<sup>635</sup> Heavy alcohol consumption<sup>633</sup> or all alcohol consumption<sup>93</sup> 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.<sup>637,640</sup> 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.<sup>636</sup>
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.<sup>642</sup> Psychosocial interventions reduced depressive symptoms not only in the stroke survivors but also in their caregivers<sup>638</sup> and may lead to reduced anxiety and improved quality of life and coping.<sup>635</sup> 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.<sup>643</sup> 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.<sup>639</sup> 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.<sup>639</sup> 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

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 B3 and B4.		
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. <sup>25,564,644-648</sup>

### 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<sup>585</sup>), 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.<sup>644</sup>

### 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.<sup>644</sup> 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.<sup>564,645</sup> 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<sup>648</sup> and can be incorporated into a risk score for predicting ICH.<sup>649</sup> 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.<sup>25</sup> 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.<sup>646,647</sup> 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.

## AHA STROKE COUNCIL SCIENTIFIC STATEMENT OVERSIGHT COMMITTEE

Joseph P. Broderick, MD, FAHA, Chair; Jose Romano, MD, FAHA, Vice Chair; Sepideh Amin-Hanjani, MD, FAHA, Immediate Past Chair; Joan Breen, MD; Cheryl Bushnell, MD, FAHA; Mandip Dhamoon, MD, DPh, FAHA; Justin Fraser, MD, FAHA; Philip B. Gorelick, MD, MPH, FAHA; Kama Guluma, MD; Richard Harvey, MD, FAHA; George Howard, DPH, FAHA; Charles Kircher, MD; Nerissa Ko, MD; William J. Mack, MD, MS, FAHA\*; Norma McNair, RN, MSN, PhD, FAHA; Peter Panagos, MD, BA, FAHA; Kevin N. Sheth, MD, FAHA†

\*AANS/CNS Liaison. †AAN Liaison.



## PRESIDENT AND STAFF: AHA/ASA

Donald M. Lloyd-Jones, MD, ScM, FAHA, President  
Nancy Brown, Chief Executive Officer  
Mariell Jessup, MD, FAHA, Chief Science and Medical Officer  
Radhika Rajgopal Singh, PhD, Senior Vice President,  
Office of Science and Medicine  
Jody Hundley, Production and Operations Manager,  
Scientific Publications, Office of Science Operations

## AHA/ASA STROKE GUIDELINES STAFF

Prashant Nedungadi, PhD, Director, Stroke Guidelines,  
Office of Science, Medicine and Health  
Melanie Stephens-Lyman, MS, Guideline Advisor—Stroke,  
Office of Science, Medicine and Health  
Anne Leonard, MPH, RN, FAHA, CCRC, Senior Science  
and Medicine Advisor, Office of Science, Medicine  
and Health

## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a

## 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)†; Phillipst; Portolat; Takedat	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

(Continued)

personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on February 15, 2022, and the American Heart Association Executive Committee on April 11, 2022. A copy of the document is available at <https://professional.heart.org/statements> by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email [Meredith.Edelman@wolterskluwer.com](mailto:Meredith.Edelman@wolterskluwer.com).


The American Heart Association requests that this document be cited as follows: Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, Hemphill JC 3rd, Johnson R, Keigher KM, Mack WJ, Mocco J, Newton EJ, Ruff IM, Sansing LH, Schulman S, Selim MH, Sheth KN, Sprigg N, Sunnerhagen KS; on behalf of the American Heart Association/American Stroke Association. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2022;53:e\*\*\*-e\*\*\*. doi: 10.1161/STR.0000000000000407

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the "Copyright Permissions Request Form" appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).



## 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	Cerebrotecht; Endostream†; Imperative Care†; Q'Apelt; Rebound Therapeutics†; Spartan Micro†; Stream Biomedical*; Truvict; Vastraxt; Viseont	Imperative Care*; Integrat; Q'Apelt; Rebound Therapeutics†; Spartan Micro†; Stream Biomedical*; Stryker*	None
J. Mocco	Mount Sinai Health System	None	None	None	None	Cerebrotecht; Corindust; CVAid*; Echovate†; Endostream†; Imperative Care†; Medtronic†; Nti†; Rebound Therapeutics†; RIST†; Serenity†; Spinaker†; Synchron†; Truvict; Vastraxt	Cerebrotecht; 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
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.

**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	TAAFT†; Friedman Brain Institutet	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

(Continued)

## Appendix 2. Continued

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	<i>Stroke, Annals of Emergency Medicine, JAMA Network Open, Academic Emergency Medicine (Reviewer)*</i>
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	Scudder Bass LLC†; Haliczzer 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	<i>Neurology (Deputy Editor)*; Seminars in Neurology (Deputy Editor)*</i>
Vasileios-Arsenios Lioutas	Harvard	None	None	None	None	None	Qmetis*	None
Demetrius Lopes	Advocate Aurora Health	None	None	Rapid Alt; Siemens†	None	Methinkst; Viz.Alt; Three Rivers†; Vastrax†; Synchron†; NDIt; Bend it†; NextGENT; Qupel†; Stryker†; Medtronic†; Asahit	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*	<i>Stroke (Editorial Board)*</i>
Stephan Mayer	Westchester Medical Center Health System	None	None	None	None	None	CSL Behring*; MaxQ Alt	None
John Oostema	Michigan State University	None	None	None	None	None	None	None

(Continued)



## Appendix 2. Continued

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	NIHT; American Hydrocephalus Association†; Focused Ultrasound Foundation†	None	None	None	NextGent; 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.

## REFERENCES

- Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639. doi: 10.1161/CIR.0000000000001052
- Flaherty ML, Woo D, Haverbusch M, Sekar P, Khoury J, Sauerbeck L, Moomaw CJ, Schneider A, Kissela B, Kleindorfer D, et al. Racial variations in location and risk of intracerebral hemorrhage. *Stroke*. 2005;36:934–937. doi: 10.1161/01.STR.0000160756.72109.95
- Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, Longwell PJ, McFarling DA, Akwumi O, Al-Wabil A, et al. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 2004;160:376–383. doi: 10.1093/aje/kwh225
- Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. World-wide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. 2009;8:355–369. doi: 10.1016/S1474-4422(09)70025-0
- Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology*. 2020;54:171–179. doi: 10.1159/000506396
- Flaherty ML, Haverbusch M, Sekar P, Kissela B, Kleindorfer D, Moomaw CJ, Sauerbeck L, Schneider A, Broderick JP, Woo D. Long-term mortality after intracerebral hemorrhage. *Neurology*. 2006;66:1182–1186. doi: 10.1212/01.wnl.0000208400.08722.7c
- Zahuranec DB, Lisabeth LD, Sánchez BN, Smith MA, Brown DL, Garcia NM, Skolarus LE, Meurer WJ, Burke JF, Adelman EE, et al. Intracerebral hemorrhage mortality is not changing despite declining incidence. *Neurology*. 2014;82:2180–2186. doi: 10.1212/WNL.0000000000000519
- Jolink WM, Klijn CJ, Brouwers PJ, Kappelle LJ, Vaartjes I. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage. *Neurology*. 2015;85:1318–1324. doi: 10.1212/WNL.0000000000002015
- van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167–176. doi: 10.1016/S1474-4422(09)70340-0
- Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, Moomaw CJ, Haverbusch M, Broderick JP. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology*. 2007;68:116–121. doi: 10.1212/01.wnl.0000250340.05202.8b
- Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0
- Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032–2060. doi: 10.1161/STR.0000000000000069
- Derdeyn CP, Zipfel GJ, Albuquerque FC, Cooke DL, Feldmann E, Sheehan JP, Torner JC; on behalf of the American Heart Association Stroke Council. Management of brain arteriovenous malformations: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e200–e224. doi: 10.1161/STR.0000000000000134
- Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–1737. doi: 10.1161/STR.0b013e3182587839
- Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, Duckwiler GR, Harris CC, Howard VJ, Johnston SC, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention; American Heart Association; American Stroke Association. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2368–2400. doi: 10.1161/STR.0000000000000070
- Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2017;48:e369]. *Stroke*. 2016;47:e98–e169. doi: 10.1161/STR.0000000000000098
- Ashcraft S, Wilson SE, Nyström KV, Dusenbury W, Wira CR, Burrus TM; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing and the Stroke Council. 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. *Stroke*. 2021;52:e164–e178. doi: 10.1161/STR.0000000000000356
- Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046
- Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, et al. 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 [published correction appears in *Stroke*. 2021;52:e483–3484]. *Stroke*. 2021;52:e364–e467. doi: 10.1161/STR.0000000000000375
- Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, Greenberg SM, Higashida RT, Kasner SE, Seshadri S; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e44–e71. doi: 10.1161/STR.0000000000000116
- Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. *Ann Neurol*. 2018;83:74–83. doi: 10.1002/ana.25123
- Graff-Radford J, Botha H, Rabinstein AA, Gunter JL, Przybelski SA, Lesnick T, Huston J 3rd, Flemming KD, Preboske GM, Senjem ML, et al. Cerebral microbleeds: prevalence and relationship to amyloid burden. *Neurology*. 2019;92:e253–e262. doi: 10.1212/WNL.00000000000006780
- Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, Krestin GP, Breteler MM. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology*. 2008;70:1208–1214. doi: 10.1212/01.wnl.0000307750.41970.d9
- Greenberg SM, Charidimou A. Diagnosis of cerebral amyloid angiopathy: evolution of the Boston criteria. *Stroke*. 2018;49:491–497. doi: 10.1161/STROKEAHA.117.016990
- Wilson D, Ambler G, Shakeshaft C, Brown MM, Charidimou A, Al-Shahi Salman R, Lip GYH, Cohen H, Banerjee G, Houlden H, et al; CROMIS-2 Collaborators. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. *Lancet Neurol*. 2018;17:539–547. doi: 10.1016/S1474-4422(18)30145-5
- Du H, Wilson D, Ambler G, Banerjee G, Shakeshaft C, Cohen H, Yousry T, Al-Shahi Salman R, Lip GYH, Houlden H, et al; Clinical Relevance of Microbleeds in Stroke (CROMIS-2) Collaborators. Small vessel disease and ischemic stroke risk during anticoagulation for atrial fibrillation after cerebral ischemia. *Stroke*. 2021;52:91–99. doi: 10.1161/STROKEAHA.120.029474
- Charidimou A, Imaizumi T, Moulin S, Biffi A, Samarasekera N, Yakushiji Y, Peeters A, Vandermeeren Y, Laloux P, Baron JC, et al.

- Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. *Neurology*. 2017;89:820–829. doi: 10.1212/WNL.0000000000004259
28. Wilkinson DA, Pandey AS, Thompson BG, Keep RF, Hua Y, Xi G. Injury mechanisms in acute intracerebral hemorrhage. *Neuropharmacology*. 2018;134(pt B):240–248. doi: 10.1016/j.neuropharm.2017.09.033
  29. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropathol Exp Neurol*. 1971;30:536–550. doi: 10.1097/00005072-197107000-00015
  30. Davis SM, Broderick J, Hennerick M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175–1181. doi: 10.1212/01.wnl.0000208408.98482.99
  31. Bray JE, Finn J, Cameron P, Smith K, Straney L, Cartledge S, Nehme Z, Lim M, Bladin C. Temporal trends in emergency medical services and general practitioner use for acute stroke after Australian public education campaigns. *Stroke*. 2018;49:3078–3080. doi: 10.1161/STROKEAHA.118.023263
  32. Ekundayo OJ, Saver JL, Fonarow GC, Schwamm LH, Xian Y, Zhao X, Hernandez AF, Peterson ED, Cheng EM. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With the Guidelines—Stroke. *Circ Cardiovasc Qual Outcomes*. 2013;6:262–269. doi: 10.1161/CIRCOUTCOMES.113.000089
  33. Jackson SL, Legvold B, Vahratian A, Blackwell DL, Fang J, Gillespie C, Hayes D, Loustalot F. Sociodemographic and geographic variation in awareness of stroke signs and symptoms among adults—United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2020;69:1617–1621. doi: 10.15585/mmwr.mm6944a1
  34. Müller-Nordhorn J, Wegscheider K, Nolte CH, Jungehülsing GJ, Rosnagel K, Reich A, Roll S, Villringer A, Willich SN. Population-based intervention to reduce prehospital delays in patients with cerebrovascular events. *Arch Intern Med*. 2009;169:1484–1490. doi: 10.1001/archinternmed.2009.232
  35. Rasura M, Baldereschi M, Di Carlo A, Di Lisi F, Patella R, Piccardi B, Polizzi B, Inzitari D; Promotion and Implementation of Stroke Care in Italy Project Working. Effectiveness of public stroke educational interventions: a review. *Eur J Neurol*. 2014;21:11–20. doi: 10.1111/ene.12266
  36. Berglund A, Svensson L, Sjöstrand C, von Arbin M, von Euler M, Wahlgren N, Engerström L, Højeberg B, Käll TB, Mjörnheim S, et al; HASTA Collaborators. Higher prehospital priority level of stroke improves thrombolysis frequency and time to stroke unit: the Hyper Acute Stroke Alarm (HASTA) study. *Stroke*. 2012;43:2666–2670. doi: 10.1161/STROKEAHA.112.652644
  37. Hsieh MJ, Chien KL, Sun JT, Tang SC, Tsai LK, Chiang WC, Chien YC, Jeng JS, Hsueh-Ming Ma M; Taipei EMS Stroke Collaborative Group. The effect and associated factors of dispatcher recognition of stroke: a retrospective observational study. *J Formos Med Assoc*. 2018;117:902–908. doi: 10.1016/j.jfma.2017.10.008
  38. Oostema JA, Carle T, Talia N, Reeves M. Dispatcher stroke recognition using a stroke screening tool: a systematic review. *Cerebrovasc Dis*. 2016;42:370–377. doi: 10.1159/000447459
  39. Oostema JA, Chassee, T, Baer, W, Edberg, A, Reeves, MJ. Accuracy and implications of hemorrhagic stroke recognition by emergency medical services. *Prehosp Emerg Care*. 2021;25:796–801. doi: 10.1080/10903127.2020.1831669
  40. Uchida K, Yoshimura S, Hiyama N, Oki Y, Matsumoto T, Tokuda R, Yamaura I, Saito S, Takeuchi M, Shigeta K, et al. Clinical prediction rules to classify types of stroke at prehospital stage. *Stroke*. 2018;49:1820–1827. doi: 10.1161/STROKEAHA.118.021794
  41. Zhelev Z, Walker G, Henschke N, Fridhandler J, Yip S. Prehospital stroke scales as screening tools for early identification of stroke and transient ischemic attack. *Cochrane Database Syst Rev*. 2019;4:CD011427. doi: 10.1002/14651858.CD011427.pub2
  42. Mochari-Greenberger H, Xian Y, Hellkamp AS, Schulte PJ, Bhatt DL, Fonarow GC, Saver JL, Reeves MJ, Schwamm LH, Smith EE. Racial/ethnic and sex differences in emergency medical services transport among hospitalized US stroke patients: analysis of the national Get With The Guidelines—Stroke Registry. *J Am Heart Assoc*. 2015;4:e002099. doi: 10.1161/JAHA.115.002099
  43. Lin CB, Peterson ED, Smith EE, Saver JL, Liang L, Xian Y, Olson DM, Shah BR, Hernandez AF, Schwamm LH, et al. Emergency medical service hospital prenotification is associated with improved evaluation and treatment of acute ischemic stroke. *Circ Cardiovasc Qual Outcomes*. 2012;5:514–522. doi: 10.1161/CIRCOUTCOMES.112.965210
  44. Patel MD, Rose KM, O'Brien EC, Rosamond WD. Prehospital notification by emergency medical services reduces delays in stroke evaluation: findings from the North Carolina Stroke Care Collaborative. *Stroke*. 2011;42:2263–2268. doi: 10.1161/STROKEAHA.110.605857
  45. Ganesh A, Lindsay P, Fang J, Kapral MK, Côté R, Joiner I, Hakim AM, Hill MD. Integrated systems of stroke care and reduction in 30-day mortality: a retrospective analysis. *Neurology*. 2016;86:898–904. doi: 10.1212/WNL.0000000000002443
  46. Helwig SA, Ragoschke-Schumm A, Schwindling L, Kettner M, Roumia S, Kulikovski J, Keller I, Manitz M, Martens D, Grün D, et al. Prehospital stroke management optimized by use of clinical scoring vs mobile stroke unit for triage of patients with stroke: a randomized clinical trial. *JAMA Neurol*. 2019;76:1484–1492. doi: 10.1001/jamaneuro.2019.2829
  47. Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlegliemien T, Roth C, Papanagiotou P, Grunwald I, Schumacher H, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol*. 2012;11:397–404. doi: 10.1016/S1474-4422(12)70057-1
  48. Slavin SJ, Sucharew H, Alwell K, Moomaw CJ, Woo D, Adeyoye O, Flaherty ML, Ferioli S, McMullan J, Mackey J, et al. Prehospital neurological deterioration in stroke. *Emerg Med J*. 2018;35:507–510. doi: 10.1136/emered-2017-207265
  49. Stiell IG, Nesbitt LP, Pickett W, Munkley D, Spaite DW, Banek J, Field B, Luinstra-Toohy L, Maloney J, Dreyer J, et al; OPALS Study Group. The OPALS Major Trauma Study: impact of advanced life-support on survival and morbidity. *CMAJ*. 2008;178:1141–1152. doi: 10.1503/cmaj.071154
  50. Gordon C, Bell R, Ranta A. Impact of the national public “FAST” campaigns. *N Z Med J*. 2019;132:48–56.
  51. Denti L, Caminiti C, Scoditti U, Zini A, Malferrari G, Zedde ML, Guidetti D, Baratti M, Vaghi L, Montanari E, et al. Impact on prehospital delay of a stroke preparedness campaign: a SW-RCT (stepped-wedge cluster randomized controlled trial). *Stroke*. 2017;48:3316–3322. doi: 10.1161/STROKEAHA.117.018135
  52. Nishijima H, Kon T, Ueno T, Haga R, Yamazaki K, Yagihashi K, Funamizu Y, Arai A, Suzuki C, Nunomura JI, et al. Effect of educational television commercial on pre-hospital delay in patients with ischemic stroke. *Neurol Sci*. 2016;37:105–109. doi: 10.1007/s10072-015-2372-1
  53. Olaiya MT, Cadilhac DA, Kim J, Ung D, Nelson MR, Srikanth VK, Bladin CF, Gerraty RP, Fitzgerald SM, Phan T, et al. Effectiveness of an intervention to improve risk factor knowledge in patients with stroke: a randomized controlled trial. *Stroke*. 2017;48:1101–1103. doi: 10.1161/STROKEAHA.116.016229
  54. Prabhakaran S, Richards CT, Kwon S, Wymore E, Song S, Eisenstein A, Brown J, Kandula NR, Mason M, Beckstrom H, et al. A community-engaged stroke preparedness intervention in Chicago. *J Am Heart Assoc*. 2020;9:e016344. doi: 10.1161/JAHA.120.016344
  55. Kim DG, Kim YJ, Shin SD, Song KJ, Lee EJ, Lee YJ, Hong KJ, Park JO, Ro YS, Park YM. Effect of emergency medical service use on time interval from symptom onset to hospital admission for definitive care among patients with intracerebral hemorrhage: a multicenter observational study. *Clin Exp Emerg Med*. 2017;4:168–177. doi: 10.15441/ceem.16.147
  56. Mosley I, Nicol M, Donnan G, Patrick I, Kerr F, Dewey H. The impact of ambulance practice on acute stroke care. *Stroke*. 2007;38:2765–2770. doi: 10.1161/STROKEAHA.107.483446
  57. Abdullah AR, Smith EE, Biddinger PD, Kalenderian D, Schwamm LH. Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. *Prehosp Emerg Care*. 2008;12:426–431. doi: 10.1080/10903120802290828
  58. Oostema JA, Nasiri M, Chassee T, Reeves MJ. The quality of prehospital ischemic stroke care: compliance with guidelines and impact on in-hospital stroke response. *J Stroke Cerebrovasc Dis*. 2014;23:2773–2779. doi: 10.1016/j.jstrokecerebrovasdis.2014.06.030
  59. Sheppard JP, Mellor RM, Greenfield S, Mant J, Quinn T, Sandler D, Sims D, Singh S, Ward M, McManus RJ; CLAHRC BBC Investigators. The association between prehospital care and in-hospital treatment decisions in acute stroke: a cohort study. *Emerg Med J*. 2015;32:93–99. doi: 10.1136/emered-2013-203026
  60. Colton K, Richards CT, Pruitt PB, Mendelson SJ, Holl JL, Naidech AM, Prabhakaran S, Maas MB. Early stroke recognition and time-based emergency care performance metrics for intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2020;29:104552. doi: 10.1016/j.jstrokecerebrovasdis.2019.104552
  61. Fan JS, Huang HH, Chen YC, Yen DH, Kao WF, Huang MS, Huang CI, Lee CH. Emergency department neurologic deterioration in patients with spontaneous intracerebral hemorrhage: incidence, predictors, and prognostic significance. *Acad Emerg Med*. 2012;19:133–138. doi: 10.1111/j.1553-2712.2011.01285.x

62. Moon JS, Janjua N, Ahmed S, Kirmani JF, Harris-Lane P, Jacob M, Ezzeddine MA, Qureshi AI. Prehospital neurologic deterioration in patients with intracerebral hemorrhage. *Crit Care Med*. 2008;36:172–175. doi: 10.1097/01.CCM.0000297876.62464.6B
63. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J, Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med*. 1999;33:373–378. doi: 10.1016/s0196-0644(99)70299-4
64. Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S. Design and retrospective analysis of the Los Angeles Prehospital Stroke Screen (LAPSS). *Prehosp Emerg Care*. 1998;2:267–273. doi: 10.1080/10903129808958878
65. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, Davis M, Ford GA. The Recognition of Stroke in the Emergency Room (ROSIER) Scale: development and validation of a stroke recognition instrument. *Lancet Neurol*. 2005;4:727–734. doi: 10.1016/S1474-4422(05)70201-5
66. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the Face Arm Speech Test. *Stroke*. 2003;34:71–76. doi: 10.1161/01.str.0000044170.46643.5e
67. Garrett MC, Komotar RJ, Starke RM, Doshi D, Otten ML, Connolly ES. Elevated troponin levels are predictive of mortality in surgical intracerebral hemorrhage patients. *Neurocrit Care*. 2010;12:199–203. doi: 10.1007/s12028-009-9245-5
68. Guo X, Li H, Zhang Z, Li S, Zhang L, Zhang J, Han G. Hyperglycemia and mortality risk in patients with primary intracerebral hemorrhage: a meta-analysis. *Mol Neurobiol*. 2016;53:2269–2275. doi: 10.1007/s12035-015-9184-4
69. He Y, Liu Q, Wang J, Wang DW, Ding H, Wang W. Prognostic value of elevated cardiac troponin I in patients with intracerebral hemorrhage. *Clin Cardiol*. 2020;43:338–345. doi: 10.1002/clc.23320
70. Zheng J, Yu Z, Ma L, Guo R, Lin S, You C, Li H. Association between blood glucose and functional outcome in intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg*. 2018;114:e756–e765. doi: 10.1016/j.wneu.2018.03.077
71. Miyagi T, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, et al. Reduced estimated glomerular filtration rate affects outcomes 3 months after intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. *J Stroke Cerebrovasc Dis*. 2015;24:176–182. doi: 10.1016/j.jstrokecerebrovasdis.2014.08.015
72. Al-Shahi Salman R, Labovitz DL, Stapf C. Spontaneous intracerebral haemorrhage. *BMJ*. 2009;339:b2586. doi: 10.1136/bmj.b2586
73. Kumar MA, Rost NS, Snider RW, Chanderraj R, Greenberg SM, Smith EE, Rosand J. Anemia and hematoma volume in acute intracerebral hemorrhage. *Crit Care Med*. 2009;37:1442–1447. doi: 10.1097/CCM.0b013e31819ced3a
74. Roh DJ, Albers DJ, Magid-Bernstein J, Doyle K, Hod E, Eisenberger A, Murthy S, Witsch J, Park S, Agarwal S, et al. Low hemoglobin and hematoma expansion after intracerebral hemorrhage. *Neurology*. 2019;93:e372–e380. doi: 10.1212/WNL.00000000000007820
75. Mrochen A, Sprügel M, Gerner ST, Sembill JA, Lang S, Lücking H, Kuramatsu JB, Huttner HB. Thrombocytopenia and clinical outcomes in intracerebral hemorrhage: a retrospective multicenter cohort study. *Stroke*. 2021;52:611–619. doi: 10.1161/STROKEAHA.120.031478
76. Beuscher VD, Sprügel M, Gerner ST, Sembill JA, Madzar D, Reindl C, Lücking H, Lang S, Hoelter P, Kuramatsu JB, et al. Chronic kidney disease and clinical outcomes in patients with intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2020;29:104802. doi: 10.1016/j.jstrokecerebrovasdis.2020.104802
77. Cutting S, Castro C, Lee VH, Prabhakaran S. Impaired renal function is not associated with increased volume of intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2014;23:86–90. doi: 10.1016/j.jstrokecerebrovasdis.2012.09.010
78. Fogelholm R, Murros K, Rissanen A, Avikainen S. Admission blood glucose and short term survival in primary intracerebral haemorrhage: a population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:349–353. doi: 10.1136/jnnp.2003.034819
79. Hao Z, Wu B, Lin S, Kong FY, Tao WD, Wang DR, Liu M. Association between renal function and clinical outcome in patients with acute stroke. *Eur Neurol*. 2010;63:237–242. doi: 10.1159/000285165
80. Rhoney DH, Parker D Jr, Millis SR, Whittaker P. Kidney dysfunction at the time of intracerebral hemorrhage is associated with increased in-hospital mortality: a retrospective observational cohort study. *Neurol Res*. 2012;34:518–521. doi: 10.1179/1743132812Y.00000000041
81. Tan X, He J, Li L, Yang G, Liu H, Tang S, Wang Y. Early hyperglycaemia and the early-term death in patients with spontaneous intracerebral haemorrhage: a meta-analysis. *Intern Med J*. 2014;44:254–260. doi: 10.1111/imj.12352
82. Salaun E, Touil A, Hubert S, Casalta JP, Gouriet F, Robinet-Borgomano E, Doche E, Laksiri N, Rey C, Lavoute C, et al. Intracranial haemorrhage in infective endocarditis. *Arch Cardiovasc Dis*. 2018;111:712–721. doi: 10.1016/j.acvd.2018.03.009
83. Ting C, Rhoten M, Dempsey J, Nichols H, Fanikos J, Ruff CT. Evaluation of direct oral anticoagulant prescribing in patients with moderate to severe renal impairment. *Clin Appl Thromb Hemost*. 2021;27:1076029620987900. doi: 10.1177/1076029620987900
84. Flaherty ML, Haverbusch M, Sekar P, Kissela BM, Kleindorfer D, Moomaw CJ, Broderick JP, Woo D. Location and outcome of anticoagulant-associated intracerebral hemorrhage. *Neurocrit Care*. 2006;5:197–201. doi: 10.1385/NCC:5:3:197
85. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology*. 2004;63:1059–1064. doi: 10.1212/01.wnl.0000138428.40673.83
86. Seiffge DJ, Goeldin MB, Tatlisumak T, Lyrer P, Fischer U, Engelter ST, Werring DJ. Meta-analysis of haematoma volume, haematoma expansion and mortality in intracerebral haemorrhage associated with oral anticoagulant use. *J Neurol*. 2019;266:3126–3135. doi: 10.1007/s00415-019-09536-1
87. Tomaselli GF, Mahaffey KW, Cuker A, Doherty PP, Doherty JU, Eikelboom JW, Fluido R, Hucker W, Mehran R, Messé SR, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70:3042–3067. doi: 10.1016/j.jacc.2017.09.1085
88. Biffi A, Battey TW, Ayres AM, Cortellini L, Schwab K, Gilson AJ, Rost NS, Viswanathan A, Goldstein JN, Greenberg SM, et al. Warfarin-related intracerebral hemorrhage: imaging and outcome. *Neurology*. 2011;77:1840–1846. doi: 10.1212/WNL.0b013e3182377e12
89. Zubkov AY, Mandrekar JN, Claassen DO, Manno EM, Wijdicks EF, Rabinstein AA. Predictors of outcome in warfarin-related intracerebral hemorrhage. *Arch Neurol*. 2008;65:1320–1325. doi: 10.1001/archneur.65.10.1320
90. Chung PW, Won YS, Kwon YJ, Choi CS, Kim BM. Initial troponin level as a predictor of prognosis in patients with intracerebral hemorrhage. *J Korean Neurosurg Soc*. 2009;45:355–359. doi: 10.3340/jkns.2009.45.6.355
91. Hays A, Diring MN. Elevated troponin levels are associated with higher mortality following intracerebral hemorrhage. *Neurology*. 2006;66:1330–1334. doi: 10.1212/01.wnl.0000210523.22944.9b
92. Sandhu R, Aronow WS, Rajdev A, Sukhija R, Amin H, D'Aquila K, Sangha A. Relation of cardiac troponin I levels with in-hospital mortality in patients with ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. *Am J Cardiol*. 2008;102:632–634. doi: 10.1016/j.amjcard.2008.04.036
93. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, et al; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3
94. Fiebach JB, Schellinger PD, Gass A, Kucinski T, Siebler M, Villringer A, Olkers P, Hirsch JG, Heiland S, Wilde P, et al; Kompetenznetzwerk Schlaganfall B5. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. *Stroke*. 2004;35:502–506. doi: 10.1161/01.STR.0000114203.75678.88
95. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, Butman JA, Patronas N, Alger JR, Latour LL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA*. 2004;292:1823–1830. doi: 10.1001/jama.292.15.1823
96. Romanova AL, Nemeth AJ, Berman MD, Guth JC, Liotta EM, Naidech AM, Maas MB. Magnetic resonance imaging versus computed tomography for identification and quantification of intraventricular hemorrhage. *J Stroke Cerebrovasc Dis*. 2014;23:2036–2040. doi: 10.1016/j.jstrokecerebrovasdis.2014.03.005
97. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1–5. doi: 10.1161/01.str.28.1.1
98. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage: incidence and time course. *Stroke*. 1996;27:1783–1787. doi: 10.1161/01.str.27.10.1783
99. Maas MB, Nemeth AJ, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Delayed intraventricular hemorrhage is common and worsens outcomes in intracerebral hemorrhage. *Neurology*. 2013;80:1295–1299. doi: 10.1212/WNL.0b013e31828ab2a7



100. AbdelFattah KR, Eastman AL, Aldy KN, Wolf SE, Minei JP, Scott WW, Madden CJ, Rickert KL, Phelan HA. A prospective evaluation of the use of routine repeat cranial CT scans in patients with intracranial hemorrhage and GCS score of 13 to 15. *J Trauma Acute Care Surg*. 2012;73:685–688. doi: 10.1097/TA.0b013e318265ccd9
101. Ding J, Yuan F, Guo Y, Chen SW, Gao WW, Wang G, Cao HL, Ju SM, Chen H, Zhang PQ, et al. A prospective clinical study of routine repeat computed tomography (CT) after traumatic brain injury (TBI). *Brain Inj*. 2012;26:1211–1216. doi: 10.3109/02699052.2012.667591
102. Maas MB, Rosenberg NF, Kosteva AR, Bauer RM, Guth JC, Liotta EM, Prabhakaran S, Naidech AM. Surveillance neuroimaging and neurologic examinations affect care for intracerebral hemorrhage. *Neurology*. 2013;81:107–112. doi: 10.1212/WNL.0b013e31829a33e4
103. Al-Shahi Salman R, Frantziadis J, Lee RJ, Lyden PD, Battley TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, et al; VISTA-ICH Collaboration; ICH Growth Individual Patient Data Meta-Analysis Collaborators. Absolute risk and predictors of the growth of acute spontaneous intracerebral hemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol*. 2018;17:885–894. doi: 10.1016/S1474-4422(18)30253-9
104. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, Kobayashi A, Boulanger JM, Lum C, Gubitz G, et al; PREDICT/Sunnybrook ICH CTA study group. Prediction of haematoma growth and outcome in patients with intracerebral hemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol*. 2012;11:307–314. doi: 10.1016/S1474-4422(12)70038-8
105. Dowlatshahi D, Brouwers HB, Demchuk AM, Hill MD, Aviv RI, Ufholz LA, Reaume M, Wintermark M, Hemphill JC 3rd, Murai Y, et al. Predicting intracerebral hemorrhage growth with the spot sign: the effect of onset-to-scan time. *Stroke*. 2016;47:695–700. doi: 10.1161/STROKEAHA.115.012012
106. Morotti A, Arba F, Boulouis G, Charidimou A. Noncontrast CT markers of intracerebral hemorrhage expansion and poor outcome: a meta-analysis. *Neurology*. 2020;95:632–643. doi: 10.1212/WNL.0000000000010660
107. Phan TG, Krishnadas N, Lai WY, Batt M, Slater LA, Chandra RV, Srikanth V, Ma H. Meta-analysis of accuracy of the spot sign for predicting hematoma growth and clinical outcomes. *Stroke*. 2019;50:2030–2036. doi: 10.1161/STROKEAHA.118.024347
108. Xu X, Zhang J, Yang K, Wang Q, Xu B, Chen X. Accuracy of spot sign in predicting hematoma expansion and clinical outcome: a meta-analysis. *Medicine (Baltimore)*. 2018;97:e11945. doi: 10.1097/MD.00000000000011945
109. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke*. 1996;27:1304–1305. doi: 10.1161/01.str.27.8.1304
110. Linfante I, Linas RH, Caplan LR, Warach S. MRI features of intracerebral hemorrhage within 2 hours from symptom onset. *Stroke*. 1999;30:2263–2267. doi: 10.1161/01.str.30.11.2263
111. Delcourt C, Huang Y, Arima H, Chalmers J, Davis SM, Heeley EL, Wang J, Parsons MW, Liu G, Anderson CS; INTERACT1 Investigators. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. *Neurology*. 2012;79:314–319. doi: 10.1212/WNL.0b013e318260cbba
112. Morotti A, Boulouis G, Dowlatshahi D, Li Q, Barras CD, Delcourt C, Yu Z, Zheng J, Zhou Z, Aviv RI, et al; International NCCT ICH Study Group. Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. *Ann Neurol*. 2019;86:480–492. doi: 10.1002/ana.25563
113. Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Silva Y, Dzialowski I, Kobayashi A, et al; the PREDICT/Sunnybrook CTA Study Group. New and expanding ventricular hemorrhage predicts poor outcome in acute intracerebral hemorrhage. *Neurology*. 2019;93:e879–e888. doi: 10.1212/WNL.0000000000008007
114. Li Q, Li R, Zhao LB, Yang XM, Yang WS, Deng L, Lv XN, Wu GF, Tang ZP, Wei M, et al. Intraventricular hemorrhage growth: definition, prevalence and association with hematoma expansion and prognosis. *Neurocrit Care*. 2020;33:732–739. doi: 10.1007/s12028-020-00958-8
115. Sifri ZC, Homnick AT, Vaynman A, Lavery R, Liao W, Mohr A, Hauser CJ, Manniker A, Livingston D. A prospective evaluation of the value of repeat cranial computed tomography in patients with minimal head injury and an intracranial bleed. *J Trauma*. 2006;61:862–867. doi: 10.1097/01.ta.0000224225.54982.90
116. Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, Delgado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN. CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke*. 2009;40:2393–2397. doi: 10.1161/STROKEAHA.108.546127
117. Hilken NA, van Asch CJJ, Werring DJ, Wilson D, Rinkel GJE, Algra A, Velthuis BK, de Kort GAP, Witkamp TD, van Nieuwenhuizen KM, et al; DIAGRAM Study Group. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. *J Neurol Neurosurg Psychiatry*. 2018;89:674–679. doi: 10.1136/jnnp-2017-317262
118. van Asch CJ, Velthuis BK, Rinkel GJ, Algra A, de Kort GA, Witkamp TD, de Ridder JC, van Nieuwenhuizen KM, de Leeuw FE, Schonewille WJ, et al; DIAGRAM Investigators. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ*. 2015;351:h5762. doi: 10.1136/bmj.h5762
119. Hilken NA, van Asch CJ, Rinkel GJ, Klijn CJ. Yield of angiographic examinations in isolated intraventricular hemorrhage: a case series and systematic review of the literature. *Eur Stroke J*. 2016;1:288–293. doi: 10.1177/2396987316666589
120. Delgado Almandoz JE, Schaefer PW, Goldstein JN, Rosand J, Lev MH, González RG, Romero JM. Practical scoring system for the identification of patients with intracerebral hemorrhage at highest risk of harboring an underlying vascular etiology: the Secondary Intracerebral Hemorrhage Score. *AJNR Am J Neuroradiol*. 2010;31:1653–1660. doi: 10.3174/ajnr.A2156
121. Olavarría VV, Bustamante G, López MJ, Lavados PM. Diagnostic accuracy of a simple clinical score to screen for vascular abnormalities in patients with intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2014;23:2069–2074. doi: 10.1016/j.jstrokecerebrovasdis.2014.03.009
122. Wilson D, Ogunbemi A, Ambler G, Jones I, Werring DJ, Jäger HR. Developing an algorithm to identify patients with intracerebral haemorrhage secondary to a macrovascular cause. *Eur Stroke J*. 2017;2:369–376. doi: 10.1177/2396987317732874
123. Kamel H, Navi BB, Hemphill JC 3rd. A rule to identify patients who require magnetic resonance imaging after intracerebral hemorrhage. *Neurocrit Care*. 2013;18:59–63. doi: 10.1007/s12028-011-9607-7
124. Lummel N, Lutz J, Brückmann H, Linn J. The value of magnetic resonance imaging for the detection of the bleeding source in non-traumatic intracerebral haemorrhages: a comparison with conventional digital subtraction angiography. *Neuroradiology*. 2012;54:673–680. doi: 10.1007/s00234-011-0953-0
125. Hino A, Fujimoto M, Yamaki T, Iwamoto Y, Katsumori T. Value of repeat angiography in patients with spontaneous subcortical hemorrhage. *Stroke*. 1998;29:2517–2521. doi: 10.1161/01.str.29.12.2517
126. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. 2018;392:1257–1268. doi: 10.1016/S0140-6736(18)31878-6
127. Cordonnier C, Klijn CJ, van Beijnum J, Al-Shahi Salman R. Radiological investigation of spontaneous intracerebral hemorrhage: systematic review and trinational survey. *Stroke*. 2010;41:685–690. doi: 10.1161/STROKEAHA.109.572495
128. Josephson CB, White PM, Krishan A, Al-Shahi Salman R. Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. *Cochrane Database Syst Rev*. 2014;2014:CD009372. doi: 10.1002/14651858.CD009372.pub2
129. Delgado Almandoz JE, Jagadeesan BD, Moran CJ, Cross DT 3rd, Zipfel GJ, Lee JM, Romero JM, Derdeyn CP. Independent validation of the secondary intracerebral hemorrhage score with catheter angiography and findings of emergent hematoma evacuation. *Neurosurgery*. 2012;70:131–140. doi: 10.1227/NEU.0b013e318222fb43
130. Flint AC, Roebken A, Singh V. Primary intraventricular hemorrhage: yield of diagnostic angiography and clinical outcome. *Neurocrit Care*. 2008;8:330–336. doi: 10.1007/s12028-008-9070-2
131. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY; on behalf of the American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:1158–1192. doi: 10.1161/STR.0b013e31820a8364
132. Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. *N Engl J Med*. 1999;340:1812–1818. doi: 10.1056/NEJM199906103402307
133. van Asch CJ, Velthuis BK, Greving JP, van Laar PJ, Rinkel GJ, Algra A, Klijn CJ. External validation of the secondary intracerebral hemorrhage score in the Netherlands. *Stroke*. 2013;44:2904–2906. doi: 10.1161/STROKEAHA.113.002386

134. Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, Nicoll JAR, Sudlow CLM, Cordonnier C, Wardlaw JM, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol*. 2018;17:232–240. doi: 10.1016/S1474-4422(18)30006-1
135. Fam MD, Pang A, Zeineddine HA, Mayo S, Stadnik A, Jesselson M, Zhang L, Dlugash R, Ziai W, Hanley D, et al; CLEAR III Trial Investigators. Demographic risk factors for vascular lesions as etiology of intraventricular hemorrhage in prospectively screened cases. *Cerebrovasc Dis*. 2017;43:223–230. doi: 10.1159/000458452
136. Charidimou A, Farid K, Baron JC. Amyloid-PET in sporadic cerebral amyloid angiopathy: a diagnostic accuracy meta-analysis. *Neurology*. 2017;89:1490–1498. doi: 10.1212/WNL.0000000000004539
137. Charidimou A, Friedrich JO, Greenberg SM, Viswanathan A. Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy: a meta-analysis. *Neurology*. 2018;90:e754–e762. doi: 10.1212/WNL.0000000000005030
138. Moullaali TJ, Wang X, Martin RH, Shipes VB, Robinson TG, Chalmers J, Suarez JI, Qureshi AI, Palesch YY, Anderson CS. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol*. 2019;18:857–864. doi: 10.1016/S1474-4422(19)30196-6
139. Li Q, Warren AD, Qureshi AI, Morotti A, Falcone GJ, Sheth KN, Shoamanesh A, Dowlatshahi D, Viswanathan A, Goldstein JN. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. *Ann Neurol*. 2020;88:388–395. doi: 10.1002/ana.25793
140. Wang X, Arima H, Heeley E, Delcourt C, Huang Y, Wang J, Stapf C, Robinson T, Woodward M, Chalmers J, et al; INTERACT2 Investigators. Magnitude of blood pressure reduction and clinical outcomes in acute intracerebral hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial study. *Hypertension*. 2015;65:1026–1032. doi: 10.1161/HYPERTENSIONAHA.114.05044
141. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, et al; INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355–2365. doi: 10.1056/NEJMoa1214609
142. Boulouis G, Morotti A, Goldstein JN, Charidimou A. Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion: systematic review and meta-analysis of randomised trials. *J Neurol Neurosurg Psychiatry*. 2017;88:339–345. doi: 10.1136/jnnp-2016-315346
143. Butcher KS, Jeerakathil T, Hill M, Demchuk AM, Dowlatshahi D, Coutts SB, Gould B, McCourt R, Asdaghi N, Findlay JM, et al; ICH ADAPT Investigators. The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure trial. *Stroke*. 2013;44:620–626. doi: 10.1161/STROKEAHA.111.000188
144. Gong S, Lin C, Zhang D, Kong X, Chen J, Wang C, Li Z, Chen R, Sheng P, Dong Y, et al. Effects of intensive blood pressure reduction on acute intracerebral hemorrhage: a systematic review and meta-analysis. *Sci Rep*. 2017;7:10694. doi: 10.1038/s41598-017-10892-z
145. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. How should we lower blood pressure after cerebral hemorrhage? A systematic review and meta-analysis. *Cerebrovasc Dis*. 2017;43:207–213. doi: 10.1159/000462986
146. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. doi: 10.1056/NEJMoa1603460
147. Wang X, Arima H, Al-Shahi Salman R, Woodward M, Heeley E, Stapf C, Lavados PM, Robinson T, Huang Y, Wang J, et al. Rapid blood pressure lowering according to recovery at different time intervals after acute intracerebral hemorrhage: pooled analysis of the INTERACT studies. *Cerebrovasc Dis*. 2015;39:242–248. doi: 10.1159/000381107
148. Qureshi AI, Foster LD, Lobanova I, Huang W, Suarez JI. Intensive blood pressure lowering in patients with moderate to severe grade acute cerebral hemorrhage: post hoc analysis of Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 Trial. *Cerebrovasc Dis*. 2020;49:244–252. doi: 10.1159/000506358
149. Arima H, Heeley E, Delcourt C, Hiraoka Y, Wang X, Woodward M, Robinson T, Stapf C, Parsons M, Lavados PM, et al; INTERACT2 Investigators; INTERACT2 Investigators. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. *Neurology*. 2015;84:464–471. doi: 10.1212/WNL.0000000000001205
150. Qureshi AI, Huang W, Lobanova I, Barsan WG, Hanley DF, Hsu CY, Lin CL, Silbergleit R, Steiner T, Suarez JI, et al; for ATACH-II Trial Investigators. Outcomes of intensive systolic blood pressure reduction in patients with intracerebral hemorrhage and excessively high initial systolic blood pressure: post hoc analysis of a randomized clinical trial. *JAMA Neurol*. 2020;77:1355–1365. doi: 10.1001/jamaneuro.2020.3075
151. Qureshi AI. The importance of acute hypertensive response in ICH. *Stroke*. 2013;44(suppl 1):S67–S69. doi: 10.1161/STROKEAHA.111.000758
152. Rodriguez-Luna D, Piñeiro S, Rubiera M, Ribo M, Coscojuela P, Pagola J, Flores A, Muchada M, Ibarra B, Meler P, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. *Eur J Neurol*. 2013;20:1277–1283. doi: 10.1111/ene.12180
153. Sakamoto Y, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, et al; SAMURAI Study Investigators. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement—Intracerebral Hemorrhage study. *Stroke*. 2013;44:1846–1851. doi: 10.1161/STROKEAHA.113.001212
154. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, Lindley R, Heeley E, Delcourt C, Neal B, et al; INTERACT2 Investigators. Blood pressure variability and outcome after acute intracerebral hemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. *Lancet Neurol*. 2014;13:364–373. doi: 10.1016/S1474-4422(14)70018-3
155. Qureshi AI, Huang W, Lobanova I, Hanley DF, Hsu CY, Malhotra K, Steiner T, Suarez JI, Toyoda K, Yamamoto H; Antihypertensive Treatment of Cerebral Hemorrhage 2 Trial Investigators. Systolic blood pressure reduction and acute kidney injury in intracerebral hemorrhage. *Stroke*. 2020;51:3030–3038. doi: 10.1161/STROKEAHA.120.030272
156. Divani AA, Liu X, Di Napoli M, Lattanzi S, Ziai W, James ML, Jafari M, Saver JL, Hemphill JC, et al. Blood pressure variability predicts poor in-hospital outcome in spontaneous intracerebral hemorrhage. *Stroke*. 2019;50:2023–2029. doi: 10.1161/STROKEAHA.119.025514
157. Bath PM, Woodhouse LJ, Krishnan K, Appleton JP, Anderson CS, Berge E, Cala L, Dixon M, England TJ, Godolphin PJ, et al. Prehospital transdermal glyceryl trinitrate for ultra-acute intracerebral hemorrhage: data from the RIGHT-2 trial. *Stroke*. 2019;50:3064–3071. doi: 10.1161/STROKEAHA.119.026389
158. Moullaali TJ, Wang X, Sandset EC, Woodhouse LJ, Law ZK, Arima H, Butcher KS, Chalmers J, Delcourt C, Edwards L, et al; Blood Pressure in Acute Stroke (BASC) Investigators. Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *J Neurol Neurosurg Psychiatry*. 2022;93:6–13. doi: 10.1136/jnnp-2021-327195
159. Ziai WC, Thompson CB, Mayo S, McBee N, Freeman WD, Dlugash R, Ullman N, Hao Y, Lane K, Awad I, et al; Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) Investigators. Intracranial hypertension and cerebral perfusion pressure insults in adult hypertensive intraventricular hemorrhage: occurrence and associations with outcome. *Crit Care Med*. 2019;47:1125–1134. doi: 10.1097/CCM.0000000000003848
160. Al-Kawaz MN, Li Y, Thompson RE, Avadhani R, de Havenon A, Gruber J, Awad I, Hanley DF, Ziai W. Intracranial pressure and cerebral perfusion pressure in large spontaneous intracranial hemorrhage and impact of minimally invasive surgery. *Front Neurol*. 2021;12:729831. doi: 10.3389/fneur.2021.729831
161. Burgess LG, Goyal N, Jones GM, Khorchid Y, Kerro A, Chapple K, Tsigoulis G, Alexandrov AV, Chang JJ. Evaluation of acute kidney injury and mortality after intensive blood pressure control in patients with intracerebral hemorrhage. *J Am Heart Assoc*. 2018;7:e008439. doi: 10.1161/JAHA.117.008439
162. Hanger HC, Geddes JA, Wilkinson TJ, Lee M, Baker AE. Warfarin-related intracerebral haemorrhage: better outcomes when reversal includes prothrombin complex concentrates. *Intern Med J*. 2013;43:308–316. doi: 10.1111/imj.12034
163. Steiner T, Poli S, Griebel M, Hüsing J, Hajda J, Freiburger A, Bendszus M, Bösel J, Christensen H, Dohmen C, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol*. 2016;15:566–573. doi: 10.1016/S1474-4422(16)00110-1
164. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost*. 2006;4:1853–1863. doi: 10.1111/j.1538-7836.2006.01986.x

165. Yasaka M, Sakata T, Minematsu K, Naritomi H. Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication. *Thromb Res.* 2002;108:25–30. doi: 10.1016/s0049-3848(02)00402-4
166. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, et al; ANNEA-4 Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med.* 2019;380:1326–1335. doi: 10.1056/NEJMoa1814051
167. Demchuk AM, Yue P, Zotova E, Nakamya J, Xu L, Milling TJ Jr, Ohara T, Goldstein JN, Middeldorp S, Verhamme P, et al. Hemostatic efficacy and anti-FXa (factor Xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEA-4 substudy. *Stroke.* 2021;52:2096–2105. doi: 10.1161/STROKEAHA.120.030565
168. Pollack CV, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam C-W, et al. Idarucizumab for dabigatran reversal: full cohort analysis. *N Engl J Med.* 2017;377:431–441. doi: 10.1056/NEJMoa1707278
169. Castillo R, Chan A, Atallah S, Derry K, Bajaj M, Zimmermann LL, Martin R, Groysman L, Stern-Nezer S, Minokadeh A, et al. Treatment of adults with intracranial hemorrhage on apixaban or rivaroxaban with prothrombin complex concentrate products. *J Thromb Thrombolysis.* 2021;51:151–158. doi: 10.1007/s11239-020-02154-z
170. Panos NG, Cook AM, John S, Jones GM; Neurocritical Care Society (NCS) Pharmacy Study Group. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. *Circulation.* 2020;141:1681–1689. doi: 10.1161/CIRCULATIONAHA.120.045769
171. Piran S, Khatib R, Schulman S, Majeed A, Holbrook A, Witt DM, Wiercioch W, Schünemann HJ, Nieuwlaat R. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. *Blood Adv.* 2019;3:158–167. doi: 10.1182/bloodadvances.2018024133
172. Ollier E, Hodin S, Lanioisélée J, Escal J, Accassat S, De Magalhaes E, Basset T, Bertoletti L, Mismetti P, Delavenne X. Effect of activated charcoal on rivaroxaban complex absorption. *Clin Pharmacokinet.* 2017;56:793–801. doi: 10.1007/s40262-016-0485-1
173. van Ryn J, Sieger P, Kink-Eiband M, Ganser D, Clemens A. Adsorption of dabigatran etexilate in water or dabigatran in pooled human plasma by activated charcoal in vitro. *Blood.* 2009;114:1065. doi: 10.1182/blood.V114.22.1065.1065
174. Wang X, Mondal S, Wang J, Tirucherai G, Zhang D, Boyd RA, Frost C. Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. *Am J Cardiovasc Drugs.* 2014;14:147–154. doi: 10.1007/s40256-013-0055-y
175. Dager WE, Roberts AJ, Nishijima DK. Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral anticoagulants. *Thromb Res.* 2019;173:71–76. doi: 10.1016/j.thromres.2018.11.009
176. Schulman S, Ritchie B, Nahriak S, Gross PL, Carrier M, Majeed A, Hwang HG, Zondag M; Study Investigators. Reversal of dabigatran-associated major bleeding with activated prothrombin concentrate: a prospective cohort study. *Thromb Res.* 2017;152:44–48. doi: 10.1016/j.thromres.2017.02.010
177. Chai-Adisaksopha C, Hillis C, Lim W, Boonyawat K, Moffat K, Crowther M. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost.* 2015;13:1790–1798. doi: 10.1111/jth.13117
178. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. *Transfus Med Rev.* 2007;21:37–48. doi: 10.1016/j.tmr.2006.08.002
179. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, Flechsenhar J, Neugebauer H, Jüttler E, Grau A, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA.* 2015;313:824–836. doi: 10.1001/jama.2015.0846
180. Parry-Jones AR, Paley L, Bray BD, Hoffman AM, James M, Cloud GC, Tyrrell RJ, Rudd AG; SSNAP Collaborative Group. Care-limiting decisions in acute stroke and association with survival: analyses of UK national quality register data. *Int J Stroke.* 2016;11:321–331. doi: 10.1177/1747493015620806
181. Carroll AH, Ramirez MP, Dowlati E, Mueller KB, Borazjani A, Chang JJ, Felbaum DR. Management of intracranial hemorrhage in patients with a left ventricular assist device: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* 2021;30:105501. doi: 10.1016/j.jstrokecerebrovasdis.2020.105501
182. Lai GY, Devlin PJ, Kesavabhotla K, Rich JD, Pham DT, Potts MB, Jahromi BS. Management and outcome of intracranial hemorrhage in patients with left ventricular assist devices. *J Neurosurg.* 2019;132:1133–1139. doi: 10.3171/2018.12.JNS182467
183. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, Goldstein JN. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation.* 2013;128:1234–1243. doi: 10.1161/CIRCULATIONAHA.113.002283
184. Laible M, Jenetzky E, Beynon C, Müller OJ, Sander P, Schüler S, Purrucker J, Möhlenbruch M, Steiner T, Veltkamp R, et al. Adverse events following international normalized ratio reversal in intracerebral hemorrhage. *Cerebrovasc Dis.* 2016;42:446–454. doi: 10.1159/000448815
185. Giovino A, Shomo E, Busey KV, Case D, Brockhurst A, Concha M. An 18-month single-center observational study of real-world use of andexanet alfa in patients with factor Xa inhibitor associated intracranial hemorrhage. *Clin Neurol Neurosurg.* 2020;195:106070. doi: 10.1016/j.clineuro.2020.106070
186. Barra ME, Das AS, Hayes BD, Rosenthal ES, Rosovsky RP, Fuh L, Patel AB, Goldstein JN, Roberts RJ. Evaluation of andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhages. *J Thromb Haemost.* 2020;18:1637–1647. doi: 10.1111/jth.14838
187. Ammar AA, Ammar MA, Owusu KA, Brown SC, Kaddouh F, Elsamadicy AA, Acosta JN, Falcone GJ. Andexanet alfa versus 4-factor prothrombin complex concentrate for reversal of factor Xa inhibitors in intracranial hemorrhage. *Neurocrit Care.* 2021;35:255–261. doi: 10.1007/s12028-020-01161-5
188. Lu G, Pine P, Leeds JM, DeGuzman F, Pratikhya P, Lin J, Malinowski J, Hollenbach SJ, Curnutte JT, Conley PB. Andexanet alfa effectively reverses edoxaban anticoagulation effects and associated bleeding in a rabbit acute hemorrhage model. *PLoS One.* 2018;13:e0195122. doi: 10.1371/journal.pone.0195122
189. Strein M, May S, Brophy GM. Anticoagulation reversal for intracranial hemorrhage in the era of the direct oral anticoagulants. *Curr Opin Crit Care.* 2020;26:122–128. doi: 10.1097/MCC.0000000000000706
190. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, et al. Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015;373:511–520. doi: 10.1056/NEJMoa1502000
191. Singh S, Nautiyal A, Belk KW. Real world outcomes associated with idarucizumab: population-based retrospective cohort study. *Am J Cardiovasc Drugs.* 2020;20:161–168. doi: 10.1007/s40256-019-00360-6
192. Gendron N, Chocron R, Billoir P, Brunier J, Camoin-Jau L, Tuffigo M, Faillie D, Teissandier D, Gay J, de Raucourt E, et al. Dabigatran level before reversal can predict hemostatic effectiveness of idarucizumab in a real-world setting. *Front Med (Lausanne).* 2020;7:599626. doi: 10.3389/fmed.2020.599626
193. Kermer P, Eschenfelder CC, Diener H-C, Grond M, Abdalla Y, Abraham A, Althaus K, Becks G, Berrouschot J, Berthel J, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany: updated series of 120 cases. *Int J Stroke.* 2020;15:609–618. doi: 10.1177/1747493019895654
194. Barco S, Lankeit M, Binder H, Schellong S, Christ M, Beyer-Westendorf J, Duerschmied D, Bauersachs R, Empen K, Held M, et al. Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: rationale and design of the HoT-PE Trial. *Thromb Haemost.* 2016;116:191–197. doi: 10.1160/TH16-01-0004
195. Eerenberg ES, Kamphuisen PW, Sijkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, cross-over study in healthy subjects. *Circulation.* 2011;124:1573–1579. doi: 10.1161/CIRCULATIONAHA.111.029017
196. Cheung YW, Barco S, Hutten BA, Meijers JC, Middeldorp S, Coppens M. In vivo increase in thrombin generation by four-factor prothrombin complex concentrate in apixaban-treated healthy volunteers. *J Thromb Haemost.* 2015;13:1799–1805. doi: 10.1111/jth.13115
197. Brown KS, Wickremasingha P, Parasurampuria DA, Weiss D, Kochan J, Dishy V, He L, Shi M. The impact of a three-factor prothrombin complex concentrate on the anticoagulatory effects of the factor Xa inhibitor edoxaban. *Thromb Res.* 2015;136:825–831. doi: 10.1016/j.thromres.2015.07.012
198. Zahir H, Brown KS, Vandell AG, Desai M, Maa JF, Dishy V, Lomeli B, Feussner A, Feng W, He L, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation.* 2015;131:82–90. doi: 10.1161/CIRCULATIONAHA.114.013445
199. Gerner ST, Kuramatsu JB, Sembill JA, Sprügel M, Endres M, Haeusler KG, Vajkoczy P, Ringleb PA, Purrucker J, Rizos T, et al; RETRACE II



- (German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage II) Investigators. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Ann Neurol*. 2018;83:186–196. doi: 10.1002/ana.25134
200. Hoffman M, Volovyk Z, Monroe DM. Reversal of dabigatran effects in models of thrombin generation and hemostasis by factor VIIa and prothrombin complex concentrate. *Anesthesiology*. 2015;122:353–362. doi: 10.1097/ALN.0000000000000540
201. Arellano-Rodrigo E, Fernandez-Gallego V, López-Vilchez I, Molina P, Díaz-Ricart M, Zafar MU, Badimon JJ, van Ryn J, Escolar G. Idarucizumab, but not procoagulant concentrates, fully restores dabigatran-altered platelet and fibrin components of hemostasis. *Transfusion*. 2019;59:2436–2445. doi: 10.1111/trf.15259
202. Arellano-Rodrigo E, Lopez-Vilchez I, Galan AM, Molina P, Reverter JC, Carné X, Villalta J, Tassies D, Lozano M, Díaz-Ricart M, et al. Coagulation factor concentrates fail to restore alterations in fibrin formation caused by rivaroxaban or dabigatran in studies with flowing blood from treated healthy volunteers. *Transfus Med Rev*. 2015;29:242–249. doi: 10.1016/j.tmr.2015.08.001
203. Drugs.com. Protamine sulfate injection. November 22, 2021. Accessed December 10, 2021. <https://www.drugs.com/pro/protamine-sulfate-injection.html>
204. van Veen JJ, Maclean RM, Hampton KK, Laidlaw S, Kitchen S, Toth P, Makris M. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis*. 2011;22:565–570. doi: 10.1097/MBC.0b013e3283494b3c
205. Ansell J, Laulicht BE, Bakhrui SH, Burnett A, Jiang X, Chen L, Baker C, Villano S, Steiner S. Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants. *Blood*. 2021;137:115–125. doi: 10.1182/blood.2020007116
206. Li X, Sun Z, Zhao W, Zhang J, Chen J, Li Y, Ye Y, Zhao J, Yang X, Xiang Y, et al. Effect of acetylsalicylic acid usage and platelet transfusion on postoperative hemorrhage and activities of daily living in patients with acute intracerebral hemorrhage. *J Neurosurg*. 2013;118:94–103. doi: 10.3171/2012.9.JNS112286
207. Feldman EA, Meola G, Zycik S, Miller CD, Krishnamurthy S, Cwikla GM, Darko W, Jennings S, Sullivan R, Seabury R. Retrospective assessment of desmopressin effectiveness and safety in patients with antiplatelet-associated intracranial hemorrhage. *Crit Care Med*. 2019;47:1759–1765. doi: 10.1097/CCM.00000000000004021
208. Mengel A, Stefanou MI, Hadaschik KA, Wolf M, Stadler V, Poli K, Lindig T, Ernemann U, Grimm F, Tatagiba M, et al. Early administration of desmopressin and platelet transfusion for reducing hematoma expansion in patients with acute antiplatelet therapy associated intracerebral hemorrhage. *Crit Care Med*. 2020;48:1009–1017. doi: 10.1097/CCM.0000000000000438
209. Schmidt KJ, Sager B, Zachariah J, Raad BF, James EG, Fletcher JJ. Cohort analysis of desmopressin effect on hematoma expansion in patients with spontaneous intracerebral hemorrhage and documented pre-ictus antiplatelet use. *J Clin Neurosci*. 2019;66:33–37. doi: 10.1016/j.jocn.2019.05.032
210. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, et al; PATCH Investigators. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387:2605–2613. doi: 10.1016/S0140-6736(16)30392-0
211. Thompson BB, Béjot Y, Caso V, Castillo J, Christensen H, Flaherty ML, Foerch C, Ghandehari K, Giroud M, Greenberg SM, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology*. 2010;75:1333–1342. doi: 10.1212/WNL.0b013e3181f735e5
212. Sprügel MI, Kuramatsu JB, Gerner ST, Sembill JA, Beuscher VD, Hagen M, Roeder SS, Lücking H, Struffert T, Dörfler A, et al. Antiplatelet therapy in primary spontaneous and oral anticoagulation-associated intracerebral hemorrhage. *Stroke*. 2018;49:2621–2629. doi: 10.1161/STROKEAHA.118.021614
213. Law ZK, Desborough M, Roberts I, Al-Shahi Salman R, England TJ, Werring DJ, Robinson T, Krishnan K, Dineen R, Laska AC, et al. Outcomes in antiplatelet-associated intracerebral hemorrhage in the TICH-2 randomized controlled trial. *J Am Heart Assoc*. 2021;10:e019130. doi: 10.1161/JAHA.120.019130
214. Desborough MJ, Oakland KA, Landoni G, Crivellari M, Doree C, Estcourt LJ, Stanworth SJ. Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2017;15:263–272. doi: 10.1111/jth.13576
215. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, Cipolle MD, Cohn CS, Fung MK, Grossman BJ, et al; AABB. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015;162:205–213. doi: 10.7326/M14-1589
216. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054. doi: 10.1136/bmj.e3054
217. Bhatt DL, Pollack CV, Weitz JI, Jennings LK, Xu S, Arnold SE, Umstead BR, Mays MC, Lee JS. Antibody-based ticagrelor reversal agent in healthy volunteers. *N Engl J Med*. 2019;380:1825–1833. doi: 10.1056/NEJMoa1901778
218. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127–2137. doi: 10.1056/NEJMoa0707534
219. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–785. doi: 10.1056/NEJMoa042991
220. Liu J, Nie X, Gu H, Zhou Q, Sun H, Tan Y, Liu D, Zheng L, Zhao J, Wang Y, et al. Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment (TRAIGE): a multicentre, randomised, placebo-controlled trial. *Stroke Vasc Neurol*. 2021;6:160–169. doi: 10.1136/svn-2021-000942
221. Meretoja A, Yassi N, Wu TY, Churilov L, Sibolt G, Jeng JS, Kleinig T, Spratt NJ, Thijs V, Wijeratne T, et al. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2020;19:980–987. doi: 10.1016/S1474-4422(20)30369-0
222. Sprigg N, Flaherty K, Appleton JP, Al-Shahi Salman R, Bereczki D, Beridze M, Christensen H, Ciccone A, Collins R, Czlonkowska A, et al; TICH-2 Investigators. Tranexamic acid for hyperacute primary Intracerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet*. 2018;391:2107–2115. doi: 10.1016/S0140-6736(18)31033-X
223. Imberti R, Pietrobono L, Klersy C, Gamba G, Iotti GA, Cornara G. Intraoperative intravenous administration of rFVIIa and hematoma volume after early surgery for spontaneous intracerebral hemorrhage: a randomized prospective phase II study. *Minerva Anestesiol*. 2012;78:168–175.
224. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; Europe/AustralAsia NovoSeven ICH Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74–79. doi: 10.1161/01.STR.0000149628.80251.b8
225. Mayer SA, Brun NC, Broderick J, Davis SM, Diringer MN, Skolnick BE, Steiner T; US NovoSeven ICH Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocrit Care*. 2006;4:206–214. doi: 10.1385/NCC.4:3:206
226. Li X, Wang YQ, Li LW. Intervention study on recombinant activated factor VIIa in depressing early hematoma extensions of cerebral hemorrhage. *Chin J N Drugs*. 2012;21:161–163. doi: 10.1161/01.STR.0000149628.80251.b8
227. Al-Shahi Salman R, Law ZK, Bath PM, Steiner T, Sprigg N. Haemostatic therapies for acute spontaneous intracerebral haemorrhage. *Cochrane Database Syst Rev*. 2018;4:CD005951. doi: 10.1002/14651858.CD005951.pub4
228. Mayer SA, Davis SM, Skolnick BE, Brun NC, Begtrup K, Broderick JP, Diringer MN, Steiner T; FAST Trial Investigators. Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor VII? *Stroke*. 2009;40:833–840. doi: 10.1161/STROKEAHA.108.524470
229. Gladstone DJ, Aviv RI, Demchuk AM, Hill MD, Thorpe KE, Khoury JC, Sucharev HJ, Al-Ajlan F, Butcher K, Dowlatshahi D, et al; SPOTLIGHT and STOP-IT Investigators and Coordinators. Effect of recombinant activated coagulation factor VII on hemorrhage expansion among patients with spot sign-positive acute intracerebral hemorrhage: the SPOTLIGHT and STOP-IT randomized clinical trials. *JAMA Neurol*. 2019;76:1493–1501. doi: 10.1001/jamaneurol.2019.2636
230. Nie X, Liu J, Liu D, Zhou Q, Duan W, Pu Y, Yang Z, Wen M, Sun H, Wang W. Haemostatic therapy in spontaneous intracerebral haemorrhage patients with high-risk of haematoma expansion by CT marker: a systematic review and meta-analysis of randomised trials. *Stroke Vasc Neurol*. 2021;6:170–179. doi: 10.1136/svn-2021-000941



231. Langhorne P, Fearon P, Ronning OM, Kaste M, Palomaki H, Vemmos K, Kalra L, Indredavik B, Blomstrand C, Rodgers H, et al; Stroke Unit Trialists' Collaboration. Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis. *Stroke*. 2013;44:3044–3049. doi: 10.1161/STROKEAHA.113.001564
232. Langhorne P, Ramachandra S; Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. *Cochrane Database Syst Rev*. 2020;4:CD000197. doi: 10.1002/14651858.CD000197.pub4
233. Parry-Jones AR, Sammut-Powell C, Paroutoglou K, Birleson E, Rowland J, Lee S, Cecchini L, Massyn M, Emsley R, Bray B, et al. An intracerebral hemorrhage care bundle is associated with lower case fatality. *Ann Neurol*. 2019;86:495–503. doi: 10.1002/ana.25546
234. Abid KA, Vail A, Patel HC, King AT, Tyrrell PJ, Parry-Jones AR. Which factors influence decisions to transfer and treat patients with acute intracerebral haemorrhage and which are associated with prognosis? A retrospective cohort study. *BMJ Open*. 2013;3:e003684. doi: 10.1136/bmjopen-2013-003684
235. Burns JD, Green DM, Lau H, Winter M, Koyfman F, DeFusco CM, Holsapple JW, Kase CS. The effect of a neurocritical care service without a dedicated neuro-ICU on quality of care in intracerebral hemorrhage. *Neurocrit Care*. 2013;18:305–312. doi: 10.1007/s12028-013-9818-1
236. Kurtz P, Fitts V, Sumer Z, Jalón H, Cooke J, Kvetan V, Mayer SA. How does care differ for neurological patients admitted to a neurocritical care unit versus a general ICU? *Neurocrit Care*. 2011;15:477–480. doi: 10.1007/s12028-011-9539-2
237. Ungerer MN, Ringleb P, Reuter B, Stock C, Ippen F, Hyrenbach S, Bruder I, Martus P, Gumbinger C; AG Schlaganfall. Stroke unit admission is associated with better outcome and lower mortality in patients with intracerebral hemorrhage. *Eur J Neurol*. 2020;27:825–832. doi: 10.1111/ene.14164
238. Terént A, Asplund K, Farahmand B, Henriksson KM, Norring B, Stegmayr B, Wester PO, Asberg KH, Asberg S; Riks-Stroke Collaboration. Stroke unit care revisited: who benefits the most? A cohort study of 105,043 patients in Riks-Stroke, the Swedish Stroke Register. *J Neurol Neurosurg Psychiatry*. 2009;80:881–887. doi: 10.1136/jnnp.2008.169102
239. Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit Care Med*. 2001;29:635–640. doi: 10.1097/00003246-200103000-00031
240. Knopf L, Staff I, Gomes J, McCullough L. Impact of a neurointensivist on outcomes in critically ill stroke patients. *Neurocrit Care*. 2012;16:63–71. doi: 10.1007/s12028-011-9620-x
241. Mirski MA, Chang CW, Cowan R. Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: evidence-based support for an intensivist-directed specialty ICU model of care. *J Neurosurg Anesthesiol*. 2001;13:83–92. doi: 10.1097/00008506-200104000-00004
242. Rincon F, Mayer SA, Rivolta J, Stillman J, Boden-Albala B, Elkind MS, Marshall R, Chong JY. Impact of delayed transfer of critically ill stroke patients from the emergency department to the neuro-ICU. *Neurocrit Care*. 2010;13:75–81. doi: 10.1007/s12028-010-9347-0
243. Saukkonen KA, Varpula M, Räsänen P, Roine RP, Voipio-Pulkki LM, Pettilä V. The effect of emergency department delay on outcome in critically ill medical patients: evaluation using hospital mortality and quality of life at 6 months. *J Intern Med*. 2006;260:586–591. doi: 10.1111/j.1365-2796.2006.01716.x
244. Stretz C, Gao C, Greer DM, Loomis C, Gilmore EJ, Kundishora AJ, Matouk CC, Hwang DY. Intracerebral hemorrhage with intraventricular extension-getting the prognosis right early. *Front Neurol*. 2017;8:418. doi: 10.3389/fneur.2017.00418
245. Maas MB, Berman MD, Guth JC, Liotta EM, Prabhakaran S, Naidech AM. Neurochecks as a biomarker of the temporal profile and clinical impact of neurologic changes after intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2015;24:2026–2031. doi: 10.1016/j.jstrokecerebrovasdis.2015.04.045
246. McLaughlin DC, Harfjes TM, Freeman WD. Sleep deprivation in neurointensive care unit patients from serial neurological checks: how much is too much? *J Neurosci Nurs*. 2018;50:205–210. doi: 10.1097/JNN.0000000000000378
247. Klaas JP, Braksick S, Mandrekar J, Sedova P, Bellolio MF, Rabinstein AA, Brown RD Jr. Factors associated with the need for intensive care unit admission following supratentorial intracerebral hemorrhage: the Triage ICH model. *Neurocrit Care*. 2017;27:75–81. doi: 10.1007/s12028-016-0346-7
248. Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A; PROSIT Study Group. Stroke-unit care for acute stroke patients: an observational follow-up study. *Lancet*. 2007;369:299–305. doi: 10.1016/S0140-6736(07)60152-4
249. Laws L, Lee F, Kumar A, Dhar R. Admitting low-risk patients with intracerebral hemorrhage to a neurological step-down unit is safe, results in shorter length of stay, and reduces intensive care utilization: a retrospective controlled cohort study. *Neurohospitalist*. 2020;10:272–276. doi: 10.1177/1941874420926760
250. Hafeez S, Behrouz R. The safety and feasibility of admitting patients with intracerebral hemorrhage to the step-down unit. *J Intensive Care Med*. 2016;31:409–411. doi: 10.1177/0885066615578113
251. Alkhachroum AM, Benthoo Q, Chari N, Kulhari A, Xiong W. Neuroscience step-down unit admission criteria for patients with intracerebral hemorrhage. *Clin Neurol Neurosurg*. 2017;162:12–15. doi: 10.1016/j.clineuro.2017.09.002
252. Jeong JH, Bang J, Jeong W, Yum K, Chang J, Hong JH, Lee K, Han MK. A dedicated neurological intensive care unit offers improved outcomes for patients with brain and spine injuries. *J Intensive Care Med*. 2019;34:104–108. doi: 10.1177/0885066617706675
253. Suarez JI, Zaidat OO, Suri MF, Feen ES, Lynch G, Hickman J, Georgiadis A, Selman WR. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. *Crit Care Med*. 2004;32:2311–2317. doi: 10.1097/01.ccm.0000146132.29042.4c
254. Sviri GE, Hayek S, Paldor I. Spontaneous cerebellar hemorrhage carries a grim prognosis in both operated and unoperated patients. *J Clin Neurosci*. 2020;78:121–127. doi: 10.1016/j.jocn.2020.05.053
255. Wartenberg KE, Wang X, Muñoz-Venturelli P, Rabinstein AA, Lavados PM, Anderson CS, Robinson T; INTERACT Investigators. Intensive care unit admission for patients in the INTERACT2 ICH blood pressure treatment trial: characteristics, predictors, and outcomes. *Neurocrit Care*. 2017;26:371–378. doi: 10.1007/s12028-016-0365-4
256. Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, et al; QASC Trialists Group. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet*. 2011;378:1699–1706. doi: 10.1016/S0140-6736(11)61485-2
257. Allen D, Rixson L. How has the impact of 'care pathway technologies' on service integration in stroke care been measured and what is the strength of the evidence to support their effectiveness in this respect? *Int J Evid Based Healthc*. 2008;6:78–110. doi: 10.1111/j.1744-1609.2007.00098.x
258. Middleton S, Coughlan K, Mnatzaganian G, Low Choy N, Dale S, Jammali-Blasi A, Levi C, Grimshaw JM, Ward J, Cadilhac DA, et al. Mortality reduction for fever, hyperglycemia, and swallowing nurse-initiated stroke intervention: QASC trial (Quality in Acute Stroke Care) follow-up. *Stroke*. 2017;48:1331–1336. doi: 10.1161/STROKEAHA.116.016038
259. Purvis T, Middleton S, Craig LE, Kilkenny MF, Dale S, Hill K, D'Este C, Cadilhac DA. Inclusion of a care bundle for fever, hyperglycaemia and swallow management in a national audit for acute stroke: evidence of upscale and spread. *Implement Sci*. 2019;14:87. doi: 10.1186/s13012-019-0934-y
260. Eltringham SA, Kilner K, Gee M, Sage K, Bray BD, Pownall S, Smith CJ. Impact of dysphagia assessment and management on risk of stroke-associated pneumonia: a systematic review. *Cerebrovasc Dis*. 2018;46:99–107. doi: 10.1159/000492730
261. Feng MC, Lin YC, Chang YH, Chen CH, Chiang HC, Huang LC, Yang YH, Hung CH. The mortality and the risk of aspiration pneumonia related with dysphagia in stroke patients. *J Stroke Cerebrovasc Dis*. 2019;28:1381–1387. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.011
262. Hinchey JA, Shephard T, Furie K, Smith D, Wang D, Tonn S; Stroke Practice Improvement Network Investigators. Formal dysphagia screening protocols prevent pneumonia. *Stroke*. 2005;36:1972–1976. doi: 10.1161/01.STR.0000177529.86868.8d
263. Hines S, Kynoch K, Munday J. Nursing interventions for identifying and managing acute dysphagia are effective for improving patient outcomes: a systematic review update. *J Neurosci Nurs*. 2016;48:215–223. doi: 10.1097/JNN.0000000000000200
264. Rai N, Prasad K, Bhatia R, Vibha D, Singh MB, Rai VK, Kumar A. Development and implementation of acute stroke care pathway in a tertiary care hospital in India: a cluster-randomized study. *Neurol India*. 2016;64 Suppl:S39–S45. doi: 10.4103/0028-3886.178038
265. Tithworth WL, Abram J, Fullerton A, Hester J, Guin P, Waters MF, Mocco J. Prospective quality initiative to maximize dysphagia screening reduces hospital-acquired pneumonia prevalence in patients with stroke. *Stroke*. 2013;44:3154–3160. doi: 10.1161/STROKEAHA.111.000204
266. Fernández-Menéndez S, García-Santiago R, Vega-Primo A, González Nafra N, Lara-Lezama LB, Redondo-Robles L, Montes-Montes

- M, Riveira-Rodríguez MC, Tejada-García J. Cardiac arrhythmias in stroke unit patients. Evaluation of the cardiac monitoring data. *Neurologia*. 2016;31:289–295. doi: 10.1016/j.nrl.2015.03.013
267. Kallmünzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, Schwab S, Köhrmann M. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors: a systematic, prospective analysis. *Stroke*. 2012;43:2892–2897. doi: 10.1161/STROKEAHA.112.664318
268. Alkhachroum AM, Miller B, Chami T, Tatsuoka C, Sila C. A troponin study on patients with ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage: type II myocardial infarction is significantly associated with stroke severity, discharge disposition and mortality. *J Clin Neurosci*. 2019;64:83–88. doi: 10.1016/j.jocn.2019.04.005
269. Lindner A, Kofler M, Rass V, Ianosi B, Gaasch M, Schiefecker AJ, Beer R, Loveys S, Rhomberg P, Pfautler B, et al. Early predictors for infectious complications in patients with spontaneous intracerebral hemorrhage and their impact on outcome. *Front Neurol*. 2019;10:817. doi: 10.3389/fneur.2019.00817
270. Morotti A, Marini S, Lena UK, Crawford K, Schwab K, Kourkoulis C, Ayres AM, Edip Guro M, Viswanathan A, Greenberg SM, et al. Significance of admission hypoalbuminemia in acute intracerebral hemorrhage. *J Neurol*. 2017;264:905–911. doi: 10.1007/s00415-017-8451-x
271. Vial F, Brunser A, Lavados P, Illanes S. Intraventricular bleeding and hematoma size as predictors of infection development in intracerebral hemorrhage: a prospective cohort study. *J Stroke Cerebrovasc Dis*. 2016;25:2708–2711. doi: 10.1016/j.jstrokecerebrovasdis.2016.07.020
272. Lord AS, Lewis A, Czeisler B, Ishida K, Torres J, Kamel H, Woo D, Elkind MS, Boden-Albala B. Majority of 30-day readmissions after intracerebral hemorrhage are related to infections. *Stroke*. 2016;47:1768–1771. doi: 10.1161/STROKEAHA.116.013229
273. Murthy SB, Moradiya Y, Shah J, Merkler AE, Mangat HS, Iadacola C, Hanley DF, Kamel H, Ziai WC. Nosocomial infections and outcomes after intracerebral hemorrhage: a population-based study. *Neurocrit Care*. 2016;25:178–184. doi: 10.1007/s12028-016-0282-6
274. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2019;50:e440–e441]. *Stroke*. 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
275. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*. 2013;382:516–524. doi: 10.1016/S0140-6736(13)61050-8
276. Yogendrakumar V, Lun R, Khan F, Salottolo K, Lacut K, Graham C, Dennis M, Hutton B, Wells PS, Fergusson D, et al. Venous thromboembolism prevention in intracerebral hemorrhage: a systematic review and network meta-analysis. *PLoS One*. 2020;15:e0234957. doi: 10.1371/journal.pone.0234957
277. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 1991;54:466–467. doi: 10.1136/jnnp.54.5.466
278. Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies. *J Thromb Haemost*. 2011;9:893–898. doi: 10.1111/j.1538-7836.2011.04241.x
279. Pan X, Li J, Xu L, Deng S, Wang Z. Safety of prophylactic heparin in the prevention of venous thromboembolism after spontaneous intracerebral hemorrhage: a meta-analysis. *J Neurol Surg A Cent Eur Neurosurg*. 2020;81:253–260. doi: 10.1055/s-0039-3400497
280. Wasay M, Khan S, Zaki KS, Khealani BA, Kamal A, Azam I, Khatri IA. A non-randomized study of safety and efficacy of heparin for DVT prophylaxis in intracerebral haemorrhage. *J Pak Med Assoc*. 2008;58:362–364.
281. Faust AC, Finch CK, Hurdle AC, Elijovich L. Early versus delayed initiation of pharmacological venous thromboembolism prophylaxis after an intracranial hemorrhage. *Neurologist*. 2017;22:166–170. doi: 10.1097/NRL.0000000000000141
282. Ianosi B, Gaasch M, Rass V, Huber L, Hackl W, Kofler M, Schiefecker AJ, Addis A, Beer R, Rhomberg P, et al. Early thrombosis prophylaxis with enoxaparin is not associated with hematoma expansion in patients with spontaneous intracerebral hemorrhage. *Eur J Neurol*. 2019;26:333–341. doi: 10.1111/ene.13830
283. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, Ridd A, Bowler G. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet*. 2009;373:1958–1965. doi: 10.1016/S0140-6736(09)60941-7
284. CLOTS (Clots in Legs or Stockings After Stroke) Trial Collaboration. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med*. 2010;153:553–562. doi: 10.7326/0003-4819-153-9-201011020-00280
285. Muriel A, Jiménez D, Aujesky D, Bertolotti L, Decousus H, Laporte S, Mismetti P, Muñoz FJ, Yusen R, Monreal M; RIETE Investigators. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. *J Am Coll Cardiol*. 2014;63:1675–1683. doi: 10.1016/j.jacc.2014.01.058
286. Byrnes MC, Irwin E, Roach R, James M, Horst PK, Reicks P. Therapeutic anticoagulation can be safely accomplished in selected patients with traumatic intracranial hemorrhage. *World J Emerg Surg*. 2012;7:25. doi: 10.1186/1749-7922-7-25
287. Matsushima K, Inaba K, Cho J, Mohammed H, Herr K, Leichtle S, Zada G, Demetriades D. Therapeutic anticoagulation in patients with traumatic brain injury. *J Surg Res*. 2016;205:186–191. doi: 10.1016/j.jss.2016.06.042
288. Goldstein JN, Fazen LE, Wendell L, Chang Y, Rost NS, Snider R, Schwab K, Chanderraj R, Kabrhel C, Kinnecom C, et al. Risk of thromboembolism following acute intracerebral hemorrhage. *Neurocrit Care*. 2009;10:28–34. doi: 10.1007/s12028-008-9134-3
289. Raslan AM, Fields JD, Bhardwaj A. Prophylaxis for venous thromboembolism in neurocritical care: a critical appraisal. *Neurocrit Care*. 2010;12:297–309. doi: 10.1007/s12028-009-9316-7
290. Sprügel M, Sembill JA, Kuramatsu JB, Gerner ST, Hagen M, Roeder SS, Endres M, Haeusler KG, Sobesky J, Schurig J, et al. Heparin for prophylaxis of venous thromboembolism in intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 2019;90:783–791. doi: 10.1136/jnnp-2018-319786
291. Ding D, Sekar P, Moomaw CJ, Comeau ME, James ML, Testai F, Flaherty ML, Vashkevich A, Worrall BB, Woo D, et al. Venous thromboembolism in patients with spontaneous intracerebral hemorrhage: a multicenter study. *Neurosurgery*. 2019;84:E304–E310. doi: 10.1093/neuros/nyy333
292. Lord AS, Gilmore E, Choi HA, Mayer SA; VISTA-ICH Collaboration. Time course and predictors of neurological deterioration after intracerebral hemorrhage. *Stroke*. 2015;46:647–652. doi: 10.1161/STROKEAHA.114.007704
293. Shirkova K, Saver JL, Starkman S, Wong G, Weng J, Hamilton S, Liebeskind DS, Eckstein M, Stratton S, Pratt F, et al; FAST-MAG Trial Coordinators and Investigators. Frequency, predictors, and outcomes of prehospital and early postarrival neurological deterioration in acute stroke: exploratory analysis of the FAST-MAG randomized clinical trial. *JAMA Neurol*. 2018;75:1364–1374. doi: 10.1001/jamaneurol.2018.1893
294. You S, Zheng D, Delcourt C, Sato S, Cao Y, Zhang S, Yang J, Wang X, Lindley RI, Robinson T, et al. Determinants of early versus delayed neurological deterioration in intracerebral hemorrhage. *Stroke*. 2019;50:1409–1414. doi: 10.1161/STROKEAHA.118.024403
295. Han KT, Kim SJ, Jang SI, Kim SJ, Lee SY, Lee HJ, Park EC. Positive correlation between care given by specialists and registered nurses and improved outcomes for stroke patients. *J Neurol Sci*. 2015;353:137–142. doi: 10.1016/j.jns.2015.04.034
296. Reynolds SS, Murray LL, McLennon SM, Bakas T. Implementation of a stroke competency program to improve nurses' knowledge of and adherence to stroke guidelines. *J Neurosci Nurs*. 2016;48:328–335. doi: 10.1097/JNN.0000000000000237
297. Tulek Z, Poulsen I, Gillis K, Jönsson AC. Nursing care for stroke patients: a survey of current practice in 11 European countries. *J Clin Nurs*. 2018;27:684–693. doi: 10.1111/jocn.14017
298. Patel MB, Bednarik J, Lee P, Shehabi Y, Salluh JI, Slooter AJ, Klein KE, Skrobik Y, Morandi A, Spronk PE, et al. Delirium monitoring in neurocritically ill patients: a systematic review. *Crit Care Med*. 2018;46:1832–1841. doi: 10.1097/CCM.0000000000000349
299. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297. doi: 10.1056/NEJMoa0810625

300. Oddo M, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapkovich ND, Levine JM, Le Roux P, Mayer SA. Impact of tight glycaemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. *Crit Care Med*. 2008;36:3233–3238. doi: 10.1097/CCM.0b013e31818f4026
301. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367. doi: 10.1056/NEJMoa011300
302. Béjot Y, Aboa-Eboulé C, Hervieu M, Jacquin A, Osseby GV, Rouaud O, Giroud M. The deleterious effect of admission hyperglycemia on survival and functional outcome in patients with intracerebral hemorrhage. *Stroke*. 2012;43:243–245. doi: 10.1161/STROKEAHA.111.632950
303. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432. doi: 10.1161/hs1001.096194
304. Kimura K, Iguchi Y, Inoue T, Shibasaki K, Matsumoto N, Kobayashi K, Yamashita S. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. *J Neurol Sci*. 2007;255:90–94. doi: 10.1016/j.jns.2007.02.005
305. Lee SH, Kim BJ, Bae HJ, Lee JS, Lee J, Park BJ, Yoon BW. Effects of glucose level on early and long-term mortality after intracerebral haemorrhage: the Acute Brain Bleeding Analysis Study. *Diabetologia*. 2010;53:429–434. doi: 10.1007/s00125-009-1617-z
306. Specogna AV, Turin TC, Patten SB, Hill MD. Factors associated with early deterioration after spontaneous intracerebral hemorrhage: a systematic review and meta-analysis. *PLoS One*. 2014;9:e96743. doi: 10.1371/journal.pone.0096743
307. Wu TY, Putaala J, Sharma G, Strbian D, Tatlisumak T, Davis SM, Meretoja A. Persistent hyperglycemia is associated with increased mortality after intracerebral hemorrhage. *J Am Heart Assoc*. 2017;6:e005760. doi: 10.1161/JAHA.117.005760
308. Kim Y, Han MH, Kim CH, Kim JM, Cheong JH, Ryu JI. Increased short-term mortality in patients with spontaneous intracerebral hemorrhage and its association with admission glucose levels and leukocytosis. *World Neurosurg*. 2017;98:503–511. doi: 10.1016/j.wneu.2016.11.087
309. Passero S, Ciacci G, Olivelli M. The influence of diabetes and hyperglycemia on clinical course after intracerebral hemorrhage. *Neurology*. 2003;61:1351–1356. doi: 10.1212/01.wnl.0000094326.30791.2d
310. Zhao Y, Yang J, Zhao H, Ding Y, Zhou J, Zhang Y. The association between hyperglycemia and the prognosis of acute spontaneous intracerebral hemorrhage. *Neurol Res*. 2017;39:152–157. doi: 10.1080/01616412.2016.1270575
311. Hervella P, Rodríguez-Yáñez M, Pumar JM, Ávila-Gómez P, da Silva-Candal A, López-Loureiro I, Rodríguez-Maqueda E, Correa-Paz C, Castillo J, Sobrino T, et al. Antihyperthermic treatment decreases perihematomal hypodensity. *Neurology*. 2020;94:e1738–e1748. doi: 10.1212/WNL.00000000000009288
312. Broessner G, Beer R, Lackner P, Helbok R, Fischer M, Pfafsler B, Rhorer J, Küppers-Tiedt L, Schneider D, Schmutzhard E. Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: bicenter prospective, randomized trial. *Stroke*. 2009;40:e657–e665. doi: 10.1161/STROKEAHA.109.557652
313. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ, Dippel DW, PAIS Investigators. The Paracetamol (Acetaminophen) in Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet Neurol*. 2009;8:434–440. doi: 10.1016/S1474-4422(09)70051-1
314. Kollmar R, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2010;41:1684–1689. doi: 10.1161/STROKEAHA.110.587758
315. Staykov D, Schwab S, Dörfler A, Kollmar R. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage: but does it influence functional outcome and mortality? *Ther Hypothermia Temp Manag*. 2011;1:105–106. doi: 10.1089/ther.2011.0004
316. Staykov D, Wagner I, Volbers B, Doerfler A, Schwab S, Kollmar R. Mild prolonged hypothermia for large intracerebral hemorrhage. *Neurocrit Care*. 2013;18:178–183. doi: 10.1007/s12028-012-9762-5
317. Volbers B, Giede-Jeppe A, Gerner ST, Sembill JA, Kuramatsu JB, Lang S, Lücking H, Staykov D, Huttner HB. Peak perihemorrhagic edema correlates with functional outcome in intracerebral hemorrhage. *Neurology*. 2018;90:e1005–e1012. doi: 10.1212/WNL.00000000000005167
318. Bush RA, Beaumont JL, Liotta EM, Maas MB, Naidech AM. Fever burden and health-related quality of life after intracerebral hemorrhage. *Neurocrit Care*. 2018;29:189–194. doi: 10.1007/s12028-018-0523-y
319. Honig A, Michael S, Eliahou R, Leker RR. Central fever in patients with spontaneous intracerebral hemorrhage: predicting factors and impact on outcome. *BMC Neurol*. 2015;15:6. doi: 10.1186/s12883-015-0258-8
320. Lord AS, Karinja S, Lantigua H, Carpenter A, Schmidt JM, Claassen J, Agarwal S, Connolly ES, Mayer SA, Badjatia N. Therapeutic temperature modulation for fever after intracerebral hemorrhage. *Neurocrit Care*. 2014;21:200–206. doi: 10.1007/s12028-013-9948-5
321. Schwarz S, Häfner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology*. 2000;54:354–361. doi: 10.1212/wnl.54.2.354
322. Iglesias-Rey R, Rodríguez-Yáñez M, Arias S, Santamaría M, Rodríguez-Castro E, López-Dequidt I, Hervella P, Sobrino T, Campos F, Castillo J. Inflammation, edema and poor outcome are associated with hyperthermia in hypertensive intracerebral hemorrhages. *Eur J Neurol*. 2018;25:1161–1168. doi: 10.1111/ene.13677
323. Elmer J, Yamane D, Hou PC, Wilcox SR, Bajwa EK, Hess DR, Camargo CA Jr, Greenberg SM, Rosand J, Pallin DJ, et al. Cost and utility of microbiological cultures early after intensive care unit admission for intracerebral hemorrhage. *Neurocrit Care*. 2017;26:58–63. doi: 10.1007/s12028-016-0285-3
324. Rincon F, Lyden P, Mayer SA. Relationship between temperature, hematoma growth, and functional outcome after intracerebral hemorrhage. *Neurocrit Care*. 2013;18:45–53. doi: 10.1007/s12028-012-9779-9
325. Mehta A, Zusman BE, Shutter LA, Choxi R, Yassin A, Antony A, Thirumala PD. The prevalence and impact of status epilepticus secondary to intracerebral hemorrhage: results from the US Nationwide Inpatient Sample. *Neurocrit Care*. 2018;28:353–361. doi: 10.1007/s12028-017-0489-1
326. Vespa PM, O'Phelan K, Shah M, Mirabelli J, Starkman S, Kidwell C, Saver J, Nuwer MR, Frazee JG, McArthur DA, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology*. 2003;60:1441–1446. doi: 10.1212/01.wnl.0000063316.47591.b4
327. Claassen J, Jetté N, Chum F, Green R, Schmidt M, Choi H, Jirsch J, Frontera JA, Connolly ES, Emerson RG, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology*. 2007;69:1356–1365. doi: 10.1212/01.wnl.00000281664.02615.6c
328. Angriman F, Tirupakuzhi Vijayaraghavan BK, Dragoi L, Lopez Soto C, Chapman M, Scales DC. Antiepileptic drugs to prevent seizures after spontaneous intracerebral hemorrhage. *Stroke*. 2019;50:1095–1099. doi: 10.1161/STROKEAHA.118.024380
329. Sheth KN, Martini SR, Moomaw CJ, Koch S, Elkind MS, Sung G, Kittner SJ, Frankel M, Rosand J, Langefeld CD, et al; ERICH Investigators. Prophylactic antiepileptic drug use and outcome in the Ethnic/Racial Variations of Intracerebral Hemorrhage study. *Stroke*. 2015;46:3532–3535. doi: 10.1161/STROKEAHA.115.010875
330. Spoelhof B, Sanchez-Bautista J, Zorrilla-Vaca A, Kaplan PW, Farrok S, Mirski M, Freund B, Rivera-Lara L. Impact of antiepileptic drugs for seizure prophylaxis on short and long-term functional outcomes in patients with acute intracerebral hemorrhage: a meta-analysis and systematic review. *Seizure*. 2019;69:140–146. doi: 10.1016/j.seizure.2019.04.017
331. Zandieh A, Messé SR, Cucchiara B, Mullen MT, Kasner SE; VISTA-ICH Collaborators. Prophylactic use of antiepileptic drugs in patients with spontaneous intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2016;25:2159–2166. doi: 10.1016/j.jstrokecerebrovasdis.2016.05.026
332. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshé SL, Peltola J, Roulet Perez E, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58:522–530. doi: 10.1111/epi.13670
- 332a. ACNS Standardized Critical Care EEG Terminology 2021: Reference Chart. American Clinical Neurophysiology Society. Accessed April 11, 2021. [https://cdn-links.lww.com/permalink/jcnp/a/jcnp\\_2020\\_12\\_21\\_fong\\_00313\\_sdc099.pdf](https://cdn-links.lww.com/permalink/jcnp/a/jcnp_2020_12_21_fong_00313_sdc099.pdf)
333. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, Lebrun L, Pirisi A, Norris JW. Seizures after stroke: a prospective multicenter study. *Arch Neurol*. 2000;57:1617–1622. doi: 10.1001/archneur.57.11.1617
334. Mehta A, Zusman BE, Choxi R, Shutter LA, Yassin A, Antony A, Thirumala PD. Seizures after intracerebral hemorrhage: incidence, risk factors, and impact on mortality and morbidity. *World Neurosurg*. 2018;112:e385–e392. doi: 10.1016/j.wneu.2018.01.052



335. Naidech AM, Garg RK, Liebling S, Levasseur K, Macken MP, Schuele SU, Batjer HH. Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke*. 2009;40:3810–3815. doi: 10.1161/STROKEAHA.109.559948
336. Gilad R, Boaz M, Dabby R, Sadeh M, Lampl Y. Are post intracerebral hemorrhage seizures prevented by anti-epileptic treatment? *Epilepsy Res*. 2011;95:227–231. doi: 10.1016/j.epilepsyres.2011.04.002
337. De Herdt V, Dumont F, Hénon H, Derambure P, Vonck K, Leys D, Cordonnier C. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. *Neurology*. 2011;77:1794–1800. doi: 10.1212/WNL.0b013e31823648a6
338. Mullen MT, Kasner SE, Messé SR. Seizures do not increase in-hospital mortality after intracerebral hemorrhage in the nationwide inpatient sample. *Neurocrit Care*. 2013;19:19–24. doi: 10.1007/s12028-012-9791-0
339. Passero S, Rocchi R, Rossi S, Ulivelli M, Vatti G. Seizures after spontaneous supratentorial intracerebral hemorrhage. *Epilepsia*. 2002;43:1175–1180. doi: 10.1046/j.1528-1157.2002.00302.x
340. Haapaniemi E, Strbian D, Rossi C, Putaala J, Sipit T, Mustanoja S, Sairanen T, Curtze S, Satopää J, Roivainen R, et al. The CAVE score for predicting late seizures after intracerebral hemorrhage. *Stroke*. 2014;45:1971–1976. doi: 10.1161/STROKEAHA.114.004686
341. Messé SR, Sansing LH, Cucchiara BL, Herman ST, Lyden PD, Kasner SE; CHANT Investigators. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocrit Care*. 2009;11:38–44. doi: 10.1007/s12028-009-9207-y
342. Naidech AM, Beaumont J, Jahromi B, Prabhakaran S, Kho A, Holl JL. Evolving use of seizure medications after intracerebral hemorrhage: a multicenter study. *Neurology*. 2017;88:52–56. doi: 10.1212/WNL.00000000000003461
343. Battey TW, Falcone GJ, Ayres AM, Schwab K, Viswanathan A, McNamara KA, DiPucchio ZY, Greenberg SM, Sheth KN, Goldstein JN, et al. Confounding by indication in retrospective studies of intracerebral hemorrhage: antiepileptic treatment and mortality. *Neurocrit Care*. 2012;17:361–366. doi: 10.1007/s12028-012-9776-z
344. Naidech AM, Beaumont J, Muldoon K, Liotta EM, Maas MB, Potts MB, Jahromi BS, Cella D, Prabhakaran S, Holl JL. Prophylactic seizure medication and health-related quality of life after intracerebral hemorrhage. *Crit Care Med*. 2018;46:1480–1485. doi: 10.1097/CCM.00000000000003272
345. Tran QK, Bzhilyanskaya V, Afridi LZ, Ahmad M, Palmer J, Rehan MA, Raffman A, Rashid A, Menne A, Pourmand A. Preventing seizure occurrence following spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of seizure prophylaxis. *Seizure*. 2021;87:46–55. doi: 10.1016/j.seizure.2021.02.029
346. Tran QK, Bzhilyanskaya V, Lurie T, Fairchild M, Rehan MA, Rashid A, Powell E, Pourmand A. Phenytoin prophylaxis and functional outcomes following spontaneous intracerebral hemorrhage: a systematic review and meta-analysis. *J Neurol Sci*. 2021;429:117624. doi: 10.1016/j.jns.2021.117624
347. Herrick DB, Ullman N, Nekoovaght-Tak S, Hanley DF, Awad I, LeDroux S, Thompson CB, Ziai WC. Determinants of external ventricular drain placement and associated outcomes in patients with spontaneous intraventricular hemorrhage. *Neurocrit Care*. 2014;21:426–434. doi: 10.1007/s12028-014-9959-x
348. Lovasik BP, McCracken DJ, McCracken CE, McDougal ME, Frerich JM, Samuels OB, Pradilla G. The effect of external ventricular drain use in intracerebral hemorrhage. *World Neurosurg*. 2016;94:309–318. doi: 10.1016/j.wneu.2016.07.022
349. Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A. Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. *J Neurol*. 2000;247:117–121. doi: 10.1007/pl00007792
350. Sumer MM, Açıkgöz B, Akpinar G. External ventricular drainage for acute obstructive hydrocephalus developing following spontaneous intracerebral haemorrhages. *Neurol Sci*. 2002;23:29–33. doi: 10.1007/s100720200020
351. Chen CJ, Ding D, Ironside N, Buell TJ, Southerland AM, Testai FD, Woo D, Worrall BB; ERICH Investigators. Intracranial pressure monitoring in patients with spontaneous intracerebral hemorrhage. *J Neurosurg*. 2019;132:1854–1864. doi: 10.3171/2019.3.JNS19545
352. Godoy DA, Núñez-Patiño RA, Zorrilla-Vaca A, Ziai WC, Hemphill JC 3rd. Intracranial hypertension after spontaneous intracerebral hemorrhage: a systematic review and meta-analysis of prevalence and mortality rate. *Neurocrit Care*. 2019;31:176–187. doi: 10.1007/s12028-018-0658-x
353. Ren J, Wu X, Huang J, Cao X, Yuan Q, Zhang D, Du Z, Zhong P, Hu J. Intracranial pressure monitoring-aided management associated with favorable outcomes in patients with hypertension-related spontaneous intracerebral hemorrhage. *Transl Stroke Res*. 2020;11:1253–1263. doi: 10.1007/s12975-020-00798-w
354. Sykora M, Steinmacher S, Steiner T, Poli S, Diedler J. Association of intracranial pressure with outcome in comatose patients with intracerebral hemorrhage. *J Neurol Sci*. 2014;342:141–145. doi: 10.1016/j.jns.2014.05.012
355. Tian Y, Wang Z, Jia Y, Li S, Wang B, Wang S, Sun L, Zhang J, Chen J, Jiang R. Intracranial pressure variability predicts short-term outcome after intracerebral hemorrhage: a retrospective study. *J Neurol Sci*. 2013;330:38–44. doi: 10.1016/j.jns.2013.04.001
356. Ziai WC, Melnychuk E, Thompson CB, Awad I, Lane K, Hanley DF. Occurrence and impact of intracranial pressure elevation during treatment of severe intraventricular hemorrhage. *Crit Care Med*. 2012;40:1601–1608. doi: 10.1097/CCM.0b013e318241e380
357. Berezcki D, Fekete I, Prado GF, Liu M, Mannitol for acute stroke. *Cochrane Database Syst Rev*. 2007;2007:CD001153. doi: 10.1002/14651858.CD001153
358. Misra UK, Kalita J, Ranjan P, Mandal SK. Mannitol in intracerebral hemorrhage: a randomized controlled study. *J Neurol Sci*. 2005;234:41–45. doi: 10.1016/j.jns.2005.03.038
359. Shah M, Birnbaum L, Rasmussen J, Sekar P, Moomaw CJ, Osborne J, Vashkevich A, Woo D. Effect of hyperosmolar therapy on outcome following spontaneous intracerebral hemorrhage: Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study. *J Stroke Cerebrovasc Dis*. 2018;27:1061–1067. doi: 10.1016/j.jstrokecerebrovasdis.2017.11.013
360. Sun S, Li Y, Zhang H, Wang X, She L, Yan Z, Lu G. The effect of mannitol in the early stage of supratentorial hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg*. 2019;124:386–396.
361. Wang X, Arima H, Yang J, Zhang S, Wu G, Woodward M, Muñoz-Venturelli P, Lavados PM, Stapf C, Robinson T, et al; INTERACT2 Investigators. Mannitol and outcome in intracerebral hemorrhage: propensity score and multivariable intensive blood pressure reduction in Acute Cerebral Hemorrhage Trial 2 results. *Stroke*. 2015;46:2762–2767. doi: 10.1161/STROKEAHA.115.009357
362. Kamel H, Navi BB, Nakagawa K, Hemphill JC 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med*. 2011;39:554–559. doi: 10.1097/CCM.0b013e318206b9be
363. Tan G, Zhou J, Yuan D, Sun S. Formula for use of mannitol in patients with intracerebral haemorrhage and high intracranial pressure. *Clin Drug Investig*. 2008;28:81–87. doi: 10.2165/00044011-200828020-00002
364. Vicenzini E, Ricciardi MC, Zucco C, Sirimarco G, Di Piero V, Lenzi GL. Effects of a single mannitol bolus on cerebral hemodynamics in intracerebral hemorrhage: a transcranial Doppler study. *Cerebrovasc Dis*. 2011;32:447–453. doi: 10.1159/000330639
365. De Reuck J, De Bleecker J, Reyntjens K. Steroid treatment in primary intracerebral haemorrhage. *Acta Neurol Belg*. 1989;89:7–11.
366. Desai P, Prasad K. Dexamethasone is not necessarily unsafe in primary supratentorial intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 1998;65:799–800. doi: 10.1136/jnnp.65.5.799a
367. Feigin VL, Anderson N, Rinkel GJ, Algra A, van Gijn J, Bennett DA. Corticosteroids for aneurysmal subarachnoid haemorrhage and primary intracerebral haemorrhage. *Cochrane Database Syst Rev*. 2005;CD004583. doi: 10.1002/14651858.CD004583.pub2
368. Pongvarin N, Bhoopat W, Viriyavejakul A, Rodprasert P, Buranasiri P, Sukondhabant S, Hensley MJ, Strom BL. Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. *N Engl J Med*. 1987;316:1229–1233. doi: 10.1056/NEJM198705143162001
369. Wintzer S, Heckmann JG, Huttner HB, Schwab S. Dexamethasone in patients with spontaneous intracerebral hemorrhage: an updated meta-analysis. *Cerebrovasc Dis*. 2020;49:495–502. doi: 10.1159/000510040
370. Adams RE, Diringner MN. Response to external ventricular drainage in spontaneous intracerebral hemorrhage with hydrocephalus. *Neurology*. 1998;50:519–523. doi: 10.1212/wnl.50.2.519
371. Steiner T, Vincent C, Morris S, Davis S, Vallejo-Torres L, Christensen MC. Neurosurgical outcomes after intracerebral hemorrhage: results of the Factor Seven for Acute Hemorrhagic Stroke Trial (FAST). *J Stroke Cerebrovasc Dis*. 2011;20:287–294. doi: 10.1016/j.jstrokecerebrovasdis.2009.12.008
372. Lee SH, Park KJ, Kang SH, Jung YG, Park JY, Park DH. Prognostic factors of clinical outcomes in patients with spontaneous thalamic hemorrhage. *Med Sci Monit*. 2015;21:2638–2646. doi: 10.12659/MSM.894132
373. Sussman ES, Kellner CP, Nelson E, McDowell MM, Bruce SS, Bruce RA, Zhuang Z, Connolly ES Jr. Hemorrhagic complications of ventriculostomy: incidence and predictors in patients with intracerebral hemorrhage. *J Neurosurg*. 2014;120:931–936. doi: 10.3171/2013.12.JNS131685



374. Kamel H, Hemphill JC 3rd. Characteristics and sequelae of intracranial hypertension after intracerebral hemorrhage. *Neurocrit Care*. 2012;17:172–176. doi: 10.1007/s12028-012-9744-7
375. Menacho ST, Grandhi R, Delic A, Anadani M, Ziai WC, Awad IA, Hanley DF, de Havenon A. Impact of intracranial pressure monitor-guided therapy on neurologic outcome after spontaneous nontraumatic intracranial hemorrhage. *J Stroke Cerebrovasc Dis*. 2021;30:105540. doi: 10.1016/j.jstrokecerebrovasdis.2020.105540
376. Wagner I, Hauer EM, Staykov D, Volbers B, Dörfler A, Schwab S, Bardutzky J. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke*. 2011;42:1540–1545. doi: 10.1161/STROKEAHA.110.609479
377. Ye H, Su Y. Hemodynamic effects of mannitol infusion in patients with acute intracerebral hemorrhage. *Acta Cir Bras*. 2013;28:106–111. doi: 10.1590/s0102-86502013000200004
378. Leasure A, Kimberly WT, Sansing LH, Kahle KT, Kronenberg G, Kunte H, Simard JM, Sheth KN. Treatment of edema associated with intracerebral hemorrhage. *Curr Treat Options Neurol*. 2016;18:9. doi: 10.1007/s11940-015-0392-z
379. Akhigbe T, Okafor U, Sattar T, Rawluk D, Fahey T. Stereotactic-guided evacuation of spontaneous supratentorial intracerebral hemorrhage: systematic review and meta-analysis. *World Neurosurg*. 2015;84:451–460. doi: 10.1016/j.wneu.2015.03.051
380. Guo G, Pan C, Guo W, Bai S, Nie H, Feng Y, Li G, Deng H, Ma Y, Zhu S, et al. Efficacy and safety of four interventions for spontaneous supratentorial intracerebral hemorrhage: a network meta-analysis. *J Neurointerv Surg*. 2020;12:598–604. doi: 10.1136/neurintsurg-2019-015362
381. Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, Mayo SW, Bistran-Hall AJ, Gandhi D, Mould WA, et al; MISTIE III Investigators. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393:1021–1032. doi: 10.1016/S0140-6736(19)30195-3
382. Li M, Mu F, Su D, Han Q, Guo Z, Chen T. Different surgical interventions for patients with spontaneous supratentorial intracranial hemorrhage: a network meta-analysis. *Clin Neurol Neurosurg*. 2020;188:105617. doi: 10.1016/j.clineuro.2019.105617
383. Scaggiante J, Zhang X, Mocco J, Kellner CP. Minimally invasive surgery for intracerebral hemorrhage. *Stroke*. 2018;49:2612–2620. doi: 10.1161/STROKEAHA.118.020688
384. Sondag L, Schreuder FHBM, Boogaarts HD, Rovers MM, Vandertop WP, Dammers R, Klijn CJM; Dutch ICH Surgery Trial Study Group, part of the CONTRAST Consortium. Neurosurgical intervention for supratentorial intracerebral hemorrhage. *Ann Neurol*. 2020;88:239–250. doi: 10.1002/ana.25732
385. Tang Y, Yin F, Fu D, Gao X, Lv Z, Li X. Efficacy and safety of minimal invasive surgery treatment in hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. *BMC Neurol*. 2018;18:136. doi: 10.1186/s12883-018-1138-9
386. Yao Z, Hu X, You C, He M. Effect and feasibility of endoscopic surgery in spontaneous intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg*. 2018;113:348–356.e2. doi: 10.1016/j.wneu.2018.02.022
387. Zhou X, Chen J, Li Q, Ren G, Yao G, Liu M, Dong Q, Guo J, Li L, Guo J, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke*. 2012;43:2923–2930. doi: 10.1161/STROKEAHA.112.667535
388. Zhou X, Xie L, Altinel Y, Qiao N. Assessment of evidence regarding minimally invasive surgery vs. conservative treatment on intracerebral hemorrhage: a trial sequential analysis of randomized controlled trials. *Front Neurol*. 2020;11:426. doi: 10.3389/fneur.2020.00426
389. Sun S, Li Y, Zhang H, Gao H, Zhou X, Xu Y, Yan K, Wang X. Neuroendoscopic surgery versus craniotomy for supratentorial hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg*. 2020;134:477–488. doi: 10.1016/j.wneu.2019.10.115
390. Xia Z, Wu X, Li J, Liu Z, Chen F, Zhang L, Zhang H, Wan X, Cheng Q. Minimally invasive surgery is superior to conventional craniotomy in patients with spontaneous supratentorial intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg*. 2018;115:266–273. doi: 10.1016/j.wneu.2018.04.181
391. Cho DY, Chen CC, Chang CS, Lee WY, Tso M. Endoscopic surgery for spontaneous basal ganglia hemorrhage: comparing endoscopic surgery, stereotactic aspiration, and craniotomy in noncomatose patients. *Surg Neurol*. 2006;65:547–555. doi: 10.1016/j.surneu.2005.09.032
392. Hattori N, Katayama Y, Maya Y, Gatherer A. Impact of stereotactic hematoma evacuation on activities of daily living during the chronic period following spontaneous putaminal hemorrhage: a randomized study. *J Neurosurg*. 2004;101:417–420. doi: 10.3171/jns.2004.101.3.0417
393. Gregson BA, Broderick JP, Auer LM, Batjer H, Chen XC, Juvela S, Morgenstern LB, Pantazis GC, Teernstra OP, Wang WZ, et al. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke*. 2012;43:1496–1504. doi: 10.1161/STROKEAHA.111.640284
394. Wang JW, Li JP, Song YL, Tan K, Wang Y, Li T, Guo P, Li X, Wang Y, Zhao QH. Stereotactic aspiration versus craniotomy for primary intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *PLoS One*. 2014;9:e107614. doi: 10.1371/journal.pone.0107614
395. Zhao XH, Zhang SZ, Feng J, Li ZZ, Ma ZL. Efficacy of neuroendoscopic surgery versus craniotomy for supratentorial hypertensive intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Brain Behav*. 2019;9:e01471. doi: 10.1002/brb3.1471
396. Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, Holzer P, Bone G, Mokry M, Körner E. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. *J Neurosurg*. 1989;70:530–535. doi: 10.3171/jns.1989.70.4.0530
397. Cho DY, Chen CC, Lee HC, Lee WY, Lin HL. Glasgow Coma Scale and hematoma volume as criteria for treatment of putaminal and thalamic intracerebral hemorrhage. *Surg Neurol*. 2008;70:628–633. doi: 10.1016/j.surneu.2007.08.006
398. Feng Y, He J, Liu B, Yang L, Wang Y. Endoscope-assisted keyhole technique for hypertensive cerebral hemorrhage in elderly patients: a randomized controlled study in 184 patients. *Turk Neurosurg*. 2016;26:84–89. doi: 10.5137/1019-5149.JTN.12669-14.0
399. Ge C, Zhao W, Guo H, Sun Z, Zhang W, Li X, Yang X, Zhang J, Wang D, Xiang Y, et al. Comparison of the clinical efficacy of craniotomy and craniopuncture therapy for the early stage of moderate volume spontaneous intracerebral haemorrhage in basal ganglia: using the CTA spot sign as an entry criterion. *Clin Neurol Neurosurg*. 2018;169:41–48. doi: 10.1016/j.clineuro.2018.04.002
400. Hanley DF, Thompson RE, Muschelli J, Rosenblum M, McBee N, Lane K, Bistran-Hall AJ, Mayo SW, Keyl P, Gandhi D, et al; MISTIE Investigators. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol*. 2016;15:1228–1237. doi: 10.1016/S1474-4422(16)30234-4
401. Kim YZ, Kim KH. Even in patients with a small hemorrhagic volume, stereotactic-guided evacuation of spontaneous intracerebral hemorrhage improves functional outcome. *J Korean Neurosurg Soc*. 2009;46:109–115. doi: 10.3340/jkns.2009.46.2.109
402. Liu H, Wu X, Tan Z, Guo H, Bai H, Wang B, Cui W, Zheng L, Sun F, Zhang X, et al. Long-term effect of endoscopic evacuation for large basal ganglia hemorrhage with GCS scores. *Front Neurol*. 2020;11:848. doi: 10.3389/fneur.2020.00848
403. Luo JB, Peng B, Quan W, Cao ZK, Xiao GC, Lu JP, Xu JM, He ZW. Therapeutic effects of aspiration with a directional soft tube and conservative treatment on mild hemorrhage in the basal ganglion [in Chinese]. *Nan Fang Yi Ke Da Xue Xue Bao*. 2008;28:1352–1353.
404. Shi J, Cai Z, Han W, Dong B, Mao Y, Cao J, Wang S, Guan W. Stereotactic catheter drainage versus conventional craniotomy for severe spontaneous intracerebral hemorrhage in the basal ganglia. *Cell Transplant*. 2019;28:1025–1032. doi: 10.1177/0963689719852302
405. Teernstra OP, Evers SM, Lodder J, Leffers P, Franke CL, Blaauw G; Multicenter Randomized Controlled Trial (SICHPA). Stereotactic Treatment of Intracerebral Hematoma by Means of a Plasminogen Activator: a multicenter randomized controlled trial (SICHPA). *Stroke*. 2003;34:968–974. doi: 10.1161/01.STR.0000063367.52044.40
406. Vespa P, Hanley D, Betz J, Hoffer A, Engh J, Carter R, Nakaji P, Ogilvy C, Jallo J, Selman W, et al; ICES Investigators. ICES (Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery) for brain hemorrhage: a multicenter randomized controlled trial. *Stroke*. 2016;47:2749–2755. doi: 10.1161/STROKEAHA.116.013837
407. Wang W, Zhou N, Wang C. Minimally invasive surgery for patients with hypertensive intracerebral hemorrhage with large hematoma volume: a retrospective study. *World Neurosurg*. 2017;105:348–358. doi: 10.1016/j.wneu.2017.05.158
408. Wang WZ, Jiang B, Liu HM, Li D, Lu CZ, Zhao YD, Sander JW. Minimally invasive craniopuncture therapy vs. conservative treatment for spontaneous

- intracerebral hemorrhage: results from a randomized clinical trial in China. *Int J Stroke*. 2009;4:11–16. doi: 10.1111/j.1747-4949.2009.00239.x
409. Xiao K, Chu H, Chen H, Zhong Y, Zhong L, Tang Y. Optimal time window for minimally invasive surgery in treating spontaneous intracerebral hemorrhage in the basal ganglia region: a multicenter and retrospective study [published online December 8, 2020]. *Br J Neurosurg*. doi: 10.1080/02688697.2020.1854682. <https://www.tandfonline.com/doi/abs/10.1080/02688697.2020.1854682?journalCode=ibjn20>
  410. Xu X, Chen X, Li F, Zheng X, Wang Q, Sun G, Zhang J, Xu B. Effectiveness of endoscopic surgery for supratentorial hypertensive intracerebral hemorrhage: a comparison with craniotomy. *J Neurosurg*. 2018;128:553–559. doi: 10.3171/2016.10.JNS161589
  411. Zhang HZ, Li YP, Yan ZC, Wang XD, She L, Wang XD, Dong L. Endoscopic evacuation of basal ganglia hemorrhage via keyhole approach using an adjustable cannula in comparison with craniotomy. *Biomed Res Int*. 2014;2014:898762. doi: 10.1155/2014/898762
  412. Zhou H, Zhang Y, Liu L, Han X, Tao Y, Tang Y, Hua W, Xue J, Dong Q. A prospective controlled study: minimally invasive stereotactic puncture therapy versus conventional craniotomy in the treatment of acute intracerebral hemorrhage. *BMC Neurol*. 2011;11:76. doi: 10.1186/1471-2377-11-76
  413. Sun H, Liu H, Li D, Liu L, Yang J, Wang W. An effective treatment for cerebral hemorrhage: minimally invasive craniopuncture combined with urokinase infusion therapy. *Neurol Res*. 2010;32:371–377. doi: 10.1179/016164110X12670144526147
  414. Kobayashi S, Sato A, Kageyama Y, Nakamura H, Watanabe Y, Yamaura A. Treatment of hypertensive cerebellar hemorrhage: surgical or conservative management? *Neurosurgery*. 1994;34:246–250.
  415. Baker AD, Rivera Perla KM, Yu Z, Dlugash R, Avadhani R, Mould WA, Ziai W, Thompson RE, Staykov D, Hanley DF. Fibrinolytic for treatment of intraventricular hemorrhage: a meta-analysis and systematic review. *Int J Stroke*. 2018;13:11–23. doi: 10.1177/1747493017730745
  416. Hanley DF, Lane K, McBee N, Ziai W, Tuhim S, Lees KR, Dawson J, Gandhi D, Ullman N, Mould WA, Mayo SW, Mendelow AD, et al; CLEAR III Investigators. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multicentre, placebo-controlled CLEAR III trial. *Lancet*. 2017;389:603–611. doi: 10.1016/S0140-6736(16)32410-2
  417. Khan NR, Tsigvoulis G, Lee SL, Jones GM, Green CS, Katsanos AH, Klimo P Jr, Arthur AS, Eljovich L, Alexandrov AV. Fibrinolysis for intraventricular hemorrhage: an updated meta-analysis and systematic review of the literature. *Stroke*. 2014;45:2662–2669. doi: 10.1161/STROKEAHA.114.005990
  418. Wang D, Liu J, Norton C, Liu M, Selim M. Local fibrinolytic therapy for intraventricular hemorrhage: a meta-analysis of randomized controlled trials. *World Neurosurg*. 2017;107:1016–1024.e1. doi: 10.1016/j.wneu.2017.07.135
  419. Mei L, Fengqun M, Qian H, Dongpo S, Zhenzhong G, Tong C. Exploration of efficacy and safety of interventions for intraventricular hemorrhage: a network meta-analysis. *World Neurosurg*. 2020;136:382–389.e6. doi: 10.1016/j.wneu.2019.10.177
  420. Li Y, Zhang H, Wang X, She L, Yan Z, Zhang N, Du R, Yan K, Xu E, Pang L. Neuroendoscopic surgery versus external ventricular drainage alone or with intraventricular fibrinolysis for intraventricular hemorrhage secondary to spontaneous supratentorial hemorrhage: a systematic review and meta-analysis. *PLoS One*. 2013;8:e80599. doi: 10.1371/journal.pone.0080599
  421. Bhattathiri PS, Gregson B, Prasad KS, Mendelow AD; STICH Investigators. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. *Acta Neurochir Suppl*. 2006;96:65–68. doi: 10.1007/s-211-30714-1\_16
  422. Naff NJ, Hanley DF, Keyl PM, Tuhim S, Kraut M, Bederson J, Bullock R, Mayer SA, Schmutzhard E. Intraventricular thrombolysis speeds blood clot resolution: results of a pilot, prospective, randomized, double-blind, controlled trial. *Neurosurgery*. 2004;54:577–583. doi: 10.1227/01.neu.0000108422.1084260
  423. King NK, Lai JL, Tan LB, Lee KK, Pang BC, Ng I, Wang E. A randomized, placebo-controlled pilot study of patients with spontaneous intraventricular haemorrhage treated with intraventricular thrombolysis. *J Clin Neurosci*. 2012;19:961–964. doi: 10.1016/j.jocn.2011.09.030
  424. Naff N, Williams MA, Keyl PM, Tuhim S, Bullock MR, Mayer SA, Coplin W, Narayan R, Haines S, Cruz-Flores S, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. *Stroke*. 2011;42:3009–3016. doi: 10.1161/STROKEAHA.110.610949
  425. Tung MY, Ong PL, Seow WT, Tan KK. A study on the efficacy of intraventricular urokinase in the treatment of intraventricular haemorrhage. *Br J Neurosurg*. 1998;12:234–239. doi: 10.1080/02688699845050
  426. Li M, Mu F, Han Q, Su D, Guo Z, Chen T. Intraventricular fibrinolysis for the treatment of intraventricular hemorrhage: a network meta-analysis. *Brain Inj*. 2020;34:864–870. doi: 10.1080/02699052.2020.1764103
  427. Chen CC, Liu CL, Tung YN, Lee HC, Chuang HC, Lin SZ, Cho DY. Endoscopic surgery for intraventricular hemorrhage (IVH) caused by thalamic hemorrhage: comparisons of endoscopic surgery and external ventricular drainage (EVD) surgery. *World Neurosurg*. 2011;75:264–268. doi: 10.1016/j.wneu.2010.07.041
  428. Zhang Z, Li X, Liu Y, Shao Y, Xu S, Yang Y. Application of neuroendoscopy in the treatment of intraventricular hemorrhage. *Cerebrovasc Dis*. 2007;24:91–96. doi: 10.1159/000103122
  429. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM; STICH II Investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*. 2013;382:397–408. doi: 10.1016/S0140-6736(13)60986-1
  430. Pantazis G, Tsitsopoulos P, Mihas C, Katsiva V, Stavrianos V, Zymaris S. Early surgical treatment vs conservative management for spontaneous supratentorial intracerebral hematomas: a prospective randomized study. *Surg Neurol*. 2006;66:492–501. doi: 10.1016/j.surneu.2006.05.054
  431. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MD, Barer DH; STICH Investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the international Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365:387–397. doi: 10.1016/S0140-6736(05)17826-X
  432. Bhaskar MK, Kumar R, Ojha B, Singh SK, Verma N, Verma R, Chandra A, Srivastava C, Jaiswal M, Jaiswal S, et al. A randomized controlled study of operative versus nonoperative treatment for large spontaneous supratentorial intracerebral hemorrhage. *Neurol India*. 2017;65:752–758. doi: 10.4103/neuroindia.NI\_151\_16
  433. Batjer HH, Reisch JS, Allen BC, Plaizier LJ, Su CJ. Failure of surgery to improve outcome in hypertensive putaminal hemorrhage: a prospective randomized trial. *Arch Neurol*. 1990;47:1103–1106. doi: 10.1001/archneur.1990.00530100071015
  434. Juvola S, Heiskanen O, Poranen A, Valtonen S, Kuurne T, Kaste M, Troupp H. The treatment of spontaneous intracerebral hemorrhage: a prospective randomized trial of surgical and conservative treatment. *J Neurosurg*. 1989;70:755–758. doi: 10.3171/jns.1989.70.5.0755
  435. McKissock W, Richardson A, Taylor J. Primary intracerebral haemorrhage: a controlled trial of surgical and conservative treatment in 180 unselected cases. *Lancet*. 1961;278:221–226.
  436. Morgenstern LB, Demchuk AM, Kim DH, Frankowski RF, Grotta JC. Rebleeding leads to poor outcome in ultra-early craniotomy for intracerebral hemorrhage. *Neurology*. 2001;56:1294–1299. doi: 10.1212/wnl.56.10.1294
  437. Morgenstern LB, Frankowski RF, Shedden P, Pasteur W, Grotta JC. Surgical treatment for intracerebral hemorrhage (STICH): a single-center, randomized clinical trial. *Neurology*. 1998;51:1359–1363. doi: 10.1212/wnl.51.5.1359
  438. Prasad K, Browman G, Srivastava A, Menon G. Surgery in primary supratentorial intracerebral hematoma: a meta-analysis of randomized trials. *Acta Neurol Scand*. 1997;95:103–110. doi: 10.1111/j.1600-0404.1997.tb00078.x
  439. Tan SH, Ng PY, Yeo TT, Wong SH, Ong PL, Venketasubramanian N. Hypertensive basal ganglia hemorrhage: a prospective study comparing surgical and nonsurgical management. *Surg Neurol*. 2001;56:287–292. doi: 10.1016/s0090-3019(01)00561-4
  440. Zuccarello M, Brott T, Derex L, Kothari R, Sauerbeck L, Tew J, Van Loveren H, Yeh HS, Tomsick T, Pancioli A, et al. Early surgical treatment for supratentorial intracerebral hemorrhage: a randomized feasibility study. *Stroke*. 1999;30:1833–1839. doi: 10.1161/01.str.30.9.1833
  441. Polster SP, Carrión-Penagos J, Lyne SB, Gregson BA, Cao Y, Thompson RE, Stadnik A, Girard R, Money PL, Lane K, et al. Intracerebral hemorrhage volume reduction and timing of intervention versus functional benefit and survival in the MISTIE III and STICH trials. *Neurosurgery*. 2021;88:961–970. doi: 10.1093/neuros/nyaa572
  442. Kuramatsu JB, Biffi A, Gerner ST, Sembill JA, Sprügel MI, Leasure A, Sansing L, Matouk C, Falcone GJ, Endres M, et al. Association of surgical hematoma evacuation vs conservative treatment with functional outcome in patients with cerebellar intracerebral hemorrhage. *JAMA*. 2019;322:1392–1403. doi: 10.1001/jama.2019.13014
  443. Singh SD, Brouwers HB, Senff JR, Pasi M, Goldstein J, Viswanathan A, Klijn CJM, Rinkel GJE. Haematoma evacuation in cerebellar intracerebral haemorrhage: systematic review. *J Neurol Neurosurg Psychiatry*. 2020;91:82–87. doi: 10.1136/jnnp-2019-321461

444. Witsch J, Neugebauer H, Zweckberger K, Jüttler E. Primary cerebellar haemorrhage: complications, treatment and outcome. *Clin Neurol Neurosurg.* 2013;115:863–869. doi: 10.1016/j.clineuro.2013.04.009
445. Auer LM, Auer T, Sayama I. Indications for surgical treatment of cerebellar haemorrhage and infarction. *Acta Neurochir (Wien).* 1986;79:74–79. doi: 10.1007/BF01407448
446. Da Pian R, Bazzan A, Pasqualin A. Surgical versus medical treatment of spontaneous posterior fossa haematomas: a cooperative study on 205 cases. *Neural Res.* 1984;6:145–151. doi: 10.1080/01616412.1984.11739680
447. Firsching R, Huber M, Frowein RA. Cerebellar haemorrhage: management and prognosis. *Neurosurg Rev.* 1991;14:191–194. doi: 10.1007/BF00310656
448. Hackenberg KA, Unterberg AW, Jung CS, Bösel J, Schönerberger S, Zweckberger K. Does suboccipital decompression and evacuation of intraparenchymal hematoma improve neurological outcome in patients with spontaneous cerebellar haemorrhage? *Clin Neurol Neurosurg.* 2017;155:22–29. doi: 10.1016/j.clineuro.2017.01.019
449. Lee TH, Huang YH, Su TM, Chen CF, Lu CH, Lee HL, Tsai HP, Sung WW, Kwan AL. Predictive factors of 2-year postoperative outcomes in patients with spontaneous cerebellar hemorrhage. *J Clin Med.* 2019;8:E818. doi: 10.3390/jcm8060818
450. Mezzadri JJ, Otero JM, Ottino CA. Management of 50 spontaneous cerebellar haemorrhages: importance of obstructive hydrocephalus. *Acta Neurochir (Wien).* 1993;122:39–44. doi: 10.1007/BF01446984
451. Shenkin HA, Zavala M. Cerebellar strokes: mortality, surgical indications, and results of ventricular drainage. *Lancet.* 1982;2:429–432. doi: 10.1016/s0140-6736(82)90453-6
452. van Loon J, Van Calenberg F, Goffin J, Plets C. Controversies in the management of spontaneous cerebellar haemorrhage: a consecutive series of 49 cases and review of the literature. *Acta Neurochir (Wien).* 1993;122:187–193. doi: 10.1007/BF01405527
453. Fung C, Murek M, Z'Graggen WJ, Krähnenbühl AK, Gautschi OP, Schucht P, Gralla J, Schaller K, Arnold M, Fischer U, et al. Decompressive hemicraniectomy in patients with supratentorial intracerebral hemorrhage. *Stroke.* 2012;43:3207–3211. doi: 10.1161/STROKEAHA.112.666537
454. Gildersleeve KL, Hirzallah MI, Esquenazi Y, Moomaw CJ, Sekar P, Cai C, Tandon N, Woo D, Gonzales NR. Hemicraniectomy for supratentorial primary intracerebral hemorrhage: a retrospective, propensity score matched study. *J Stroke Cerebrovasc Dis.* 2019;28:104361. doi: 10.1016/j.jstrokecerebrovasdis.2019.104361
455. Heuts G, Bruce SS, Zacharia BE, Hickman ZL, Kellner CP, Sussman ES, McDowell MM, Bruce RA, Connolly ES Jr. Decompressive hemicraniectomy without clot evacuation in dominant-sided intracerebral hemorrhage with ICP crisis. *Neurosurg Focus.* 2013;34:E4. doi: 10.3171/2013.2.FOCUS1326
456. Iwuchukwu I, Bui C, Hsieh B, Sabharwal V, Mohammed A, McGrade H, Biro E, Nguyen D, Sulaiman O. Decompressive hemicraniectomy in the management of subcortical spontaneous intracerebral hemorrhage. *Int J Neurosci.* 2020;130:965–971. doi: 10.1080/00207454.2020.1713773
457. Lo YT, See AAQ, King NKK. Decompressive craniectomy in spontaneous intracerebral hemorrhage: a case-control study. *World Neurosurg.* 2017;103:815–820.e2. doi: 10.1016/j.wneu.2017.04.025
458. Moussa WM, Khedr W. Decompressive craniectomy and expansive duraplasty with evacuation of hypertensive intracerebral hematoma, a randomized controlled trial. *Neurosurg Rev.* 2017;40:115–127. doi: 10.1007/s10143-016-0743-6
459. Pedro KM, Chua AE, Lapitan MCM. Decompressive hemicraniectomy without clot evacuation in spontaneous intracranial hemorrhage: A systematic review. *Clin Neurol Neurosurg.* 2020;192:105730. doi: 10.1016/j.clineuro.2020.105730
460. Yao Z, Ma L, You C, He M. Decompressive craniectomy for spontaneous intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg.* 2018;110:121–128. doi: 10.1016/j.wneu.2017.10.167
461. Li L, Molian VA, Seaman SC, Zanaty M, Howard MA, Greenlee JD, Hasan DM, Leira EC. Impact of intracerebral hematoma evacuation during decompressive hemicraniectomy on functional outcomes. *Stroke.* 2021;52:1105–1108. doi: 10.1161/STROKEAHA.120.032224
462. Rasras S, Safari H, Zeinali M, Jahangiri M. Decompressive hemicraniectomy without clot evacuation in supratentorial deep-seated intracerebral hemorrhage. *Clin Neurol Neurosurg.* 2018;174:1–6. doi: 10.1016/j.clineuro.2018.08.017
463. Ghani AR, John JT, Idris Z, Ghazali MM, Murshid NL, Musa KI. Functional outcome at 6 months in surgical treatment of spontaneous supratentorial intracerebral haemorrhage. *Malays J Med Sci.* 2008;15:48–55.
464. Hayes SB, Benveniste RJ, Morcos JJ, Aziz-Sultan MA, Elhannady MS. Retrospective comparison of craniotomy and decompressive craniectomy for surgical evacuation of nontraumatic, supratentorial intracerebral hemorrhage. *Neurosurg Focus.* 2013;34:E3. doi: 10.3171/2013.2.FOCUS12422
465. Hegde A, Prasad GL, Menon G. Decompressive craniectomy in spontaneous intracerebral hemorrhage: a comparison with standard craniotomy using propensity-matched analysis. *World Neurosurg.* 2020;144:e622–e630. doi: 10.1016/j.wneu.2020.09.016
466. Kim DB, Park SK, Moon BH, Cho BR, Jang DK, Jang KS. Comparison of craniotomy and decompressive craniectomy in large supratentorial intracerebral hemorrhage. *J Clin Neurosci.* 2018;50:208–213. doi: 10.1016/j.jocn.2018.01.066
467. Li Q, Yang CH, Xu JG, Li H, You C. Surgical treatment for large spontaneous basal ganglia hemorrhage: retrospective analysis of 253 cases. *Br J Neurosurg.* 2013;27:617–621. doi: 10.3109/02688697.2013.765938
468. Ma L, Liu WG, Sheng HS, Fan J, Hu WW, Chen JS. Decompressive craniectomy in addition to hematoma evacuation improves mortality of patients with spontaneous basal ganglia hemorrhage. *J Stroke Cerebrovasc Dis.* 2010;19:294–298. doi: 10.1016/j.jstrokecerebrovasdis.2009.07.002
469. Maira G, Anile C, Colosimo C, Rossi GF. Surgical treatment of primary supratentorial intracerebral hemorrhage in stuporous and comatose patients. *Neural Res.* 2002;24:54–60. doi: 10.1179/016164102101199549
470. Satter AR, Islam MR, Haque MR, Mahmood E, Rahman MZ, Barman N, Rahman MA. Comparison between decompressive craniectomy with durotomy and conservative treatment in spontaneous supratentorial intracerebral hemorrhage. *Mymensingh Med J.* 2016;25:316–325.
471. Shimamura N, Munakata A, Naraoka M, Nakano T, Ohkuma H. Decompressive hemicraniectomy is not necessary to rescue supratentorial hypertensive intracerebral hemorrhage patients: consecutive single-center experience. *Acta Neurochir Suppl.* 2011;111:415–419. doi: 10.1007/978-3-7091-0693-8\_71
472. Gregório T, Pipa S, Cavaleiro P, Atanásio G, Albuquerque I, Castro Chaves P, Azevedo L. Original intracerebral hemorrhage score for the prediction of short-term mortality in cerebral hemorrhage: systematic review and meta-analysis. *Crit Care Med.* 2019;47:857–864. doi: 10.1097/CCM.00000000000003744
473. Gregório T, Pipa S, Cavaleiro P, Atanásio G, Albuquerque I, Chaves PC, Azevedo L. Assessment and comparison of the four most extensively validated prognostic scales for intracerebral hemorrhage: systematic review with meta-analysis. *Neurocrit Care.* 2019;30:449–466. doi: 10.1007/s12028-018-0633-6
474. Gregório T, Pipa S, Cavaleiro P, Atanásio G, Albuquerque I, Chaves PC, Azevedo L. Prognostic models for intracerebral hemorrhage: systematic review and meta-analysis. *BMC Med Res Methodol.* 2018;18:145. doi: 10.1186/s12874-018-0613-8
475. Hwang DY, Dell CA, Sparks MJ, Watson TD, Langefeld CD, Comeau ME, Rosand J, Battey TW, Koch S, Perez ML, et al. Clinician judgment vs formal scales for predicting intracerebral hemorrhage outcomes. *Neurology.* 2016;86:126–133. doi: 10.1212/WNL.00000000000002266
476. Zahuranec DB, Morgenstern LB, Sánchez BN, Resnicow K, White DB, Hemphill JC 3rd. Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology.* 2010;75:626–633. doi: 10.1212/WNL.0b013e3181ed9cc9
477. Sembill JA, Gerner ST, Volbers B, Bobinger T, Lücking H, Kloska SP, Schwab S, Huttner HB, Kuramatsu JB. Severity assessment in maximally treated ICH patients: the max-ICH score. *Neurology.* 2017;89:423–431. doi: 10.1212/WNL.00000000000004174
478. Sembill JA, Castello JP, Sprügel MI, Gerner ST, Hoelter P, Lücking H, Doerfler A, Schwab S, Huttner HB, Biffi A, et al. Multicenter validation of the max-ICH score in intracerebral hemorrhage. *Ann Neurol.* 2021;89:474–484. doi: 10.1002/ana.25969
479. Hemphill JC 3rd, Newman J, Zhao S, Johnston SC. Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage. *Stroke.* 2004;35:1130–1134. doi: 10.1161/01.STR.0000125858.71051.ca
480. Madhok DY, Vitt JR, Maclsaac D, Hsia RY, Kim AS, Hemphill JC. Early do-not-resuscitate orders and outcome after intracerebral hemorrhage. *Neurocrit Care.* 2021;34:492–499. doi: 10.1007/s12028-020-01014-1
481. Morgenstern LB, Zahuranec DB, Sánchez BN, Becker KJ, Geraghty M, Hughes R, Norris G, Hemphill JC 3rd. Full medical support for intracerebral hemorrhage. *Neurology.* 2015;84:1739–1744. doi: 10.1212/WNL.0000000000001525
482. Reznik ME, Moody S, Murray K, Costa S, Groy BM, Madsen TE, Mahta A, Wendell LC, Thompson BB, Rao SS, et al. The impact of delirium on



- withdrawal of life-sustaining treatment after intracerebral hemorrhage. *Neurology*. 2020;95:e2727–e2735. doi: 10.1212/WNL.00000000000010738
483. Yang TC, Li JG, Guo W. Do not resuscitate orders for patients with intracerebral hemorrhage: experience from a Chinese tertiary care center. *Eur Neurol*. 2015;73:144–149. doi: 10.1159/000369792
484. Zahuranec DB, Brown DL, Lisabeth LD, Gonzales NR, Longwell PJ, Smith MA, Garcia NM, Morgenstern LB. Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology*. 2007;68:1651–1657. doi: 10.1212/01.wnl.0000261906.93238.72
485. Sahgal S, Yande A, Thompson BB, Chen EP, Fagerlin A, Morgenstern LB, Zahuranec DB. Surrogate satisfaction with decision making after intracerebral hemorrhage. *Neurocrit Care*. 2021;34:193–200. doi: 10.1007/s12028-020-01018-x
486. Minhas JS, Sammut-Powell C, Birlerson E, Patel HC, Parry-Jones AR. Are do-not-resuscitate orders associated with limitations of care beyond their intended purpose in patients with acute intracerebral haemorrhage? Analysis of the ABC-ICH study. *BMJ Open Qual*. 2021;10:e001113. doi: 10.1136/bmjopen-2020-001113
487. Silvennoinen K, Meretoja A, Strbian D, Putaala J, Kaste M, Tatlisumak T. Do-not-resuscitate (DNR) orders in patients with intracerebral hemorrhage. *Int J Stroke*. 2014;9:53–58. doi: 10.1111/ijvs.12161
488. Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, Winn HR, Longstreth WT Jr. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766–772. doi: 10.1212/wnl.56.6.766
489. Creutzfeldt CJ, Becker KJ, Weinstein JR, Khot SP, McPharlin TO, Ton TG, Longstreth WT Jr, Tirschwell DL. Do-not-attempt-resuscitation orders and prognostic models for intraparenchymal hemorrhage. *Crit Care Med*. 2011;39:158–162. doi: 10.1097/CCM.0b013e3181fb7b49
490. Langhorne P, Baylan S; Early Supported Discharge Trialists. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev*. 2017;7:CD000443. doi: 10.1002/14651858.CD000443.pub4
491. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarria VV, Muñoz Venturelli P, Brunser A, Peng B, Cui L, et al; HeadPoST Investigators and Coordinators. Cluster-randomized, crossover trial of head positioning in acute stroke. *N Engl J Med*. 2017;376:2437–2447. doi: 10.1056/NEJMoa1615715
492. Liu N, Cadilhac DA, Andrew NE, Zeng L, Li Z, Li J, Li Y, Yu X, Mi B, Li Z, et al. Randomized controlled trial of early rehabilitation after intracerebral hemorrhage stroke: difference in outcomes within 6 months of stroke. *Stroke*. 2014;45:3502–3507. doi: 10.1161/STROKEAHA.114.005661
493. FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *Lancet*. 2019;393:265–274. doi: 10.1016/S0140-6736(18)32823-X
494. AFFINITY Trial Collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2020;19:651–660. doi: 10.1016/S1474-4422(20)30207-6
495. Legg LA, Tilney R, Hsieh CF, Wu S, Lundstrom E, Rudberg AS, Kutlubaev MA, Dennis M, Soleimani B, Barugh A, Hackett, ML, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev*. 2019;2019:1–159. doi: 10.1002/14651858.CD009286.pub3
496. EFFECTS Trial Collaboration. Safety and efficacy of fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2020;19:661–669. doi: 10.1016/S1474-4422(20)30219-2
497. Marquez-Romero JM, Reyes-Martínez M, Huerta-Franco MR, Ruiz-Franco A, Silos H, Arauz A. Fluoxetine for motor recovery after acute intracerebral hemorrhage: the FMRICH trial. *Clin Neurol Neurosurg*. 2020;190:105656. doi: 10.1016/j.clineuro.2019.105656
498. Bernhardt J, Borschmann K, Collier JM, Thrift AG, Langhorne P, Middleton S, Lindley RI, Dewey HM, Bath P, Said CM, et al; AVERT Trialists Collaboration Group. Fatal and non-fatal events within 14 days after early, intensive mobilization post stroke. *Neurology*. 2020;96:e1156–e1166. doi: 10.1212/WNL.00000000000011106
499. Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, Collier J, Churilov L, Moodie M, Dewey H, Donnan G. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet*. 2015;386:46–55. doi: 10.1016/S0140-6736(15)60690-0
500. Langhorne P, Pollock A; Stroke Unit Trialists' Collaboration. What are the components of effective stroke unit care? *Age Ageing*. 2002;31:365–371. doi: 10.1093/ageing/31.5.365
501. Widén Holmqvist L, von Koch L, Kostulas V, Holm M, Widsell G, Tegler H, Johansson K, Almazán J, de Pedro-Cuesta J. A randomized controlled trial of rehabilitation at home after stroke in southwest Stockholm. *Stroke*. 1998;29:591–597. doi: 10.1161/01.str.29.3.591
502. Mayo NE, Wood-Dauphinee S, Côté R, Gayton D, Carlton J, Buttery J, Tamblyn R. There's no place like home: an evaluation of early supported discharge for stroke. *Stroke*. 2000;31:1016–1023. doi: 10.1161/01.str.31.5.1016
503. Anderson C, Rubenach S, Murchu CN, Clark M, Spencer C, Winsor A. Home or hospital for stroke rehabilitation? Results of a randomized controlled trial, I: health outcomes at 6 months. *Stroke*. 2000;31:1024–1031. doi: 10.1161/01.str.31.5.1024
504. Indredavik B, Fjaertoft H, Ekeberg G, Løge AD, Mørch B. Benefit of an extended stroke unit service with early supported discharge: a randomized, controlled trial. *Stroke*. 2000;31:2989–2994. doi: 10.1161/01.str.31.12.2989
505. Suwanwela NC, Phanthumchinda K, Limtongkul S, Suvanprakorn P; Thai Red Cross Volunteers Bureau. Comparison of short (3-day) hospitalization followed by home care treatment and conventional (10-day) hospitalization for acute ischemic stroke. *Cerebrovasc Dis*. 2002;13:267–271. doi: 10.1159/000057854
506. Donnelly M, Power M, Russell M, Fullerton K. Randomized controlled trial of an early discharge rehabilitation service: the Belfast Community Stroke Trial. *Stroke*. 2004;35:127–133. doi: 10.1161/01.STR.0000106911.96026.8F
507. Burton L, Tyson SF. Screening for cognitive impairment after stroke: a systematic review of psychometric properties and clinical utility. *J Rehabil Med*. 2015;47:193–203. doi: 10.2340/16501977-1930
508. Kubiszewski P, Sugita L, Kourkoulis C, DiPucchio Z, Schwab K, Anderson CD, Gurol ME, Greenberg SM, Viswanathan A, Rosand J, et al. Association of selective serotonin reuptake inhibitor use after intracerebral hemorrhage with hemorrhage recurrence and depression severity. *JAMA Neurol*. 2020;78:1–8. doi: 10.1001/jamaneuro.2020.3142
509. Meader N, Moe-Byrne T, Llewellyn A, Mitchell AJ. Screening for poststroke major depression: a meta-analysis of diagnostic validity studies. *J Neurol Neurosurg Psychiatry*. 2014;85:198–206. doi: 10.1136/jnnp-2012-304194
510. Lees R, Selvarajah J, Fenton C, Pendlebury ST, Langhorne P, Stott DJ, Quinn TJ. Test accuracy of cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke. *Stroke*. 2014;45:3008–3018. doi: 10.1161/STROKEAHA.114.005842
511. Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. *Cochrane Database Syst Rev*. 2019;3:CD013069. doi: 10.1002/14651858.CD013069.pub2
512. Chung CS, Pollock A, Campbell T, Durward BR, Hagen S. Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage. *Cochrane Database Syst Rev*. 2013:CD008391. doi: 10.1002/14651858.CD008391.pub2
513. Loetscher T, Potter KJ, Wong D, das Nair R. Cognitive rehabilitation for attention deficits following stroke. *Cochrane Database Syst Rev*. 2019;2019:1–57.
514. Nair RD, Lincoln NB. Cognitive rehabilitation for memory deficits following stroke. *Cochrane Database Syst Rev*. 2007:CD002293. doi: 10.1002/14651858.CD002293.pub3
515. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst Rev*. 2012:CD005562. doi: 10.1002/14651858.CD005562.pub2
516. Hackman DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. *Neurology*. 2012;79:1862–1865. doi: 10.1212/WNL.0b013e318271f848
517. Jensen MP, Ziff OJ, Banerjee G, Ambler G, Werring DJ. The impact of selective serotonin reuptake inhibitors on the risk of intracranial haemorrhage: a systematic review and meta-analysis. *Eur Stroke J*. 2019;4:144–152. doi: 10.1177/2396987319827211
518. Liu L, Fuller M, Behymer TP, Ng Y, Christianson T, Shah S, King NKK, Woo D, James ML. Selective serotonin reuptake inhibitors and intracerebral hemorrhage risk and outcome. *Stroke*. 2020;51:1135–1141. doi: 10.1161/STROKEAHA.119.028406
519. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*. 2018;6:CD001190. doi: 10.1002/14651858.CD001190.pub3
520. Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database Syst Rev*. 2004:CD004395. doi: 10.1002/14651858.CD004395.pub2
521. McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J. Memantine for dementia. *Cochrane Database Syst Rev*. 2019;3:CD003154. doi: 10.1002/14651858.CD003154.pub6
522. Christensen MC, Mayer SA, Ferran JM, Kissela B. Depressed mood after intracerebral hemorrhage: the FAST trial. *Cerebrovasc Dis*. 2009;27:353–360. doi: 10.1159/000202012



523. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2014;9:1017–1025. doi: 10.1111/ijis.12357
524. Donnellan C, Werring D. Cognitive impairment before and after intracerebral haemorrhage: a systematic review. *Neurol Sci*. 2020;41:509–527. doi: 10.1007/s10072-019-04150-5
525. Moulin S, Labreuche J, Bombois S, Rossi C, Boulouis G, Hénon H, Duhamel A, Leys D, Cordonnier C. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *Lancet Neurol*. 2016;15:820–829. doi: 10.1016/S1474-4422(16)00130-7
526. Patel M, Coshall C, Rudd AG, Wolfe CD. Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clin Rehabil*. 2003;17:158–166. doi: 10.1191/0269215503cr5960a
527. Kapoor A, Lancot KL, Bayley M, Herrmann N, Murray BJ, Swartz RH. Screening for post-stroke depression and cognitive impairment at baseline predicts long-term patient-centered outcomes after stroke. *J Geriatr Psychiatry Neurol*. 2019;32:40–48. doi: 10.1177/0891988718819859
528. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102–109. doi: 10.1016/j.arr.2019.01.013
529. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. *Stroke*. 2013;44:1105–1110. doi: 10.1161/STROKEAHA.111.679340
530. Bartoli F, Di Brita C, Crocamo C, Clerici M, Carrà G. Early post-stroke depression and mortality: meta-analysis and meta-regression. *Front Psychiatry*. 2018;9:530. doi: 10.3389/fpsy.2018.00530
531. Bartoli F, Lillia N, Lax A, Crocamo C, Mantero V, Carrà G, Agostoni E, Clerici M. Depression after stroke and risk of mortality: a systematic review and meta-analysis. *Stroke Res Treat*. 2013;2013:862978. doi: 10.1155/2013/862978
532. Kowalska K, Krzywozański Ł, Droś J, Pasińska P, Wilk A, Klimkowicz-Mrowiec A. Early depression independently of other neuropsychiatric conditions, influences disability and mortality after stroke (research study-part of PROPOLIS study). *Biomedicine*. 2020;8:E509. doi: 10.3390/biomedicine8110509
533. Kutlubaev MA, Hackett ML. Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. *Int J Stroke*. 2014;9:1026–1036. doi: 10.1111/ijis.12356
534. Schmid AA, Kroenke K, Hendrie HC, Bakas T, Sutherland JM, Williams LS. Poststroke depression and treatment effects on functional outcomes. *Neurology*. 2011;76:1000–1005. doi: 10.1212/WNL.0b013e318210435e
535. van de Port IG, Kwakkel G, van Wijk I, Lindeman E. Susceptibility to deterioration of mobility long-term after stroke: a prospective cohort study. *Stroke*. 2006;37:167–171. doi: 10.1161/01.STR.0000195180.69904.f2
536. Eriksson M, Glader EL, Norrving B, Asplund K. Poststroke suicide attempts and completed suicides: a socioeconomic and nationwide perspective. *Neurology*. 2015;84:1732–1738. doi: 10.1212/WNL.0000000000001514
537. Patel MD, Coshall C, Rudd AG, Wolfe CD. Cognitive impairment after stroke: clinical determinants and its associations with long-term stroke outcomes. *J Am Geriatr Soc*. 2002;50:700–706. doi: 10.1046/j.1532-5415.2002.501165.x
538. Barba R, Morin MD, Cemillán C, Delgado C, Domingo J, Del Ser T. Previous and incident dementia as risk factors for mortality in stroke patients. *Stroke*. 2002;33:1993–1998. doi: 10.1161/01.str.0000017285.73172.91
539. Jamieson EI, Newman D, Metcalf AK, Naguib MF, Saada J, Potter JF, Myint PK. Dementia is strongly associated with 90-day mortality in lobar cerebral amyloid angiopathy related intra-cerebral haemorrhage. *J Neural Sci*. 2012;322:161–165. doi: 10.1016/j.jns.2012.07.047
540. Allida S, Cox KL, Hsieh CF, Lang H, House A, Hackett ML. Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression after stroke. *Cochrane Database Syst Rev*. 2020;1:CD003437. doi: 10.1002/14651858.CD003437.pub4
541. Wang SB, Wang YY, Zhang QE, Wu SL, Ng CH, Ungvari GS, Chen L, Wang CX, Jia FJ, Xiang YT. Cognitive behavioral therapy for post-stroke depression: a meta-analysis. *J Affect Disord*. 2018;235:589–596. doi: 10.1016/j.jad.2018.04.011
542. Knapp P, Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, Chun HY, Lewis SR. Interventions for treating anxiety after stroke. *Cochrane Database Syst Rev*. 2017;5:CD008860. doi: 10.1002/14651858.CD008860.pub3
543. Deng L, Qiu S, Yang Y, Wang L, Li Y, Lin J, Wei Q, Yang L, Wang D, Liu M. Efficacy and tolerability of pharmacotherapy for post-stroke depression: a network meta-analysis. *Oncotarget*. 2018;9:23718–23728. doi: 10.18632/oncotarget.23891
544. Deng L, Sun X, Qiu S, Xiong Y, Li Y, Wang L, Wei Q, Wang D, Liu M. Interventions for management of post-stroke depression: a bayesian network meta-analysis of 23 randomized controlled trials. *Sci Rep*. 2017;7:16466. doi: 10.1038/s41598-017-16663-0
545. Qin B, Chen H, Gao W, Zhao LB, Zhao MJ, Qin HX, Chen W, Chen L, Yang MX. Efficacy, acceptability, and tolerability of antidepressant treatments for patients with post-stroke depression: a network meta-analysis. *Braz J Med Biol Res*. 2018;51:e7218. doi: 10.1590/1414-431x20187218
546. Sun Y, Liang Y, Jiao Y, Lin J, Qu H, Xu J, Zhao C. Comparative efficacy and acceptability of antidepressant treatment in poststroke depression: a multiple-treatments meta-analysis. *BMJ Open*. 2017;7:e016499. doi: 10.1136/bmjopen-2017-016499
547. Tan S, Huang X, Ding L, Hong H. Efficacy and safety of citalopram in treating post-stroke depression: a meta-analysis. *Eur Neurol*. 2015;74:188–201. doi: 10.1159/000441446
548. Xu XM, Zou DZ, Shen LY, Liu Y, Zhou XY, Pu JC, Dong MX, Wei YD. Efficacy and feasibility of antidepressant treatment in patients with post-stroke depression. *Medicine (Baltimore)*. 2016;95:e5349. doi: 10.1097/MD.0000000000005349
549. Chollet F, Tardy J, Albuher JF, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol*. 2011;10:123–130. doi: 10.1016/S1474-4422(10)70314-8
550. Shao D, Zhao ZN, Zhang YQ, Zhou XY, Zhao LB, Dong M, Xu FH, Xiang YJ, Luo HY. Efficacy of repetitive transcranial magnetic stimulation for post-stroke depression: a systematic review and meta-analysis of randomized clinical trials. *Braz J Med Biol Res*. 2021;54:e10010. doi: 10.1590/1414-431X202010010
551. Williams LS, Kroenke K, Bakas T, Plue LD, Brizendine E, Tu W, Hendrie H. Care management of poststroke depression: a randomized, controlled trial. *Stroke*. 2007;38:998–1003. doi: 10.1161/01.STR.0000257319.14023.61
552. Godefroy O, Fickl A, Roussel M, Auribault C, Bugnicourt JM, Lamy C, Canape S, Petitnicolas G. Is the Montreal Cognitive Assessment superior to the Mini-Mental State Examination to detect poststroke cognitive impairment? A study with neuropsychological evaluation. *Stroke*. 2011;42:1712–1716. doi: 10.1161/STROKEAHA.110.606277
553. Swartz RH, Bayley M, Lancôt KL, Murray BJ, Cayley ML, Lien K, Sicard MN, Thorpe KE, Dowlatshahi D, Mandzia JL, et al. Post-stroke depression, obstructive sleep apnea, and cognitive impairment: rationale for, and barriers to, routine screening. *Int J Stroke*. 2016;11:509–518. doi: 10.1177/1747493016641968
554. Meeks JR, Bambhroliya AB, Sheth SA, Khan B, Slooter AJC, Ely EW, Miller CC, Tyson JE, McCullough LD, Savitz SI, et al. Long-term cognitive impairment associated with delirium in acute neurological injury. *Crit Care Explor*. 2020;2:e0130. doi: 10.1097/CCE.0000000000000130
555. Rosenthal LJ, Francis BA, Beaumont JL, Cella D, Berman MD, Maas MB, Liotta EM, Askew R, Naidech AM. Agitation, delirium, and cognitive outcomes in intracerebral hemorrhage. *Psychosomatics*. 2017;58:19–27. doi: 10.1016/j.psym.2016.07.004
556. Carrion C, Aymerich M, Baillés E, López-Bermejo A. Cognitive psychosocial intervention in dementia: a systematic review. *Dement Geriatr Cogn Disord*. 2013;36:363–375. doi: 10.1159/000354365
557. Carrion C, Folkvord F, Anastasiadou D, Aymerich M. Cognitive therapy for dementia patients: a systematic review. *Dement Geriatr Cogn Disord*. 2018;46:1–26. doi: 10.1159/000490851
558. Chollet F, Rigal J, Marque P, Barbieuc-Guillot M, Raposo N, Fabry V, Albuher JF, Pariente J, Loubinoux I. Serotonin selective reuptake inhibitors (SSRIs) and stroke. *Curr Neurol Neurosci Rep*. 2018;18:100. doi: 10.1007/s11910-018-0904-9
559. Douros A, Ades M, Renoux C. Risk of intracranial hemorrhage associated with the use of antidepressants inhibiting serotonin reuptake: a systematic review. *CNS Drugs*. 2018;32:321–334. doi: 10.1007/s40263-018-0507-7
560. Renoux C, Vahey S, Dell'Aniello S, Boivin JF. Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. *JAMA Neurol*. 2017;74:173–180. doi: 10.1001/jamaneurol.2016.4529
561. Deleted in proof.
562. Azarpazhooh MR, Nicol MB, Donnan GA, Dewey HM, Sturm JW, Macdonnell RA, Pearce DC, Thrift AG. Patterns of stroke recurrence according to subtype of first stroke event: the North East Melbourne Stroke Incidence Study (NEMESIS). *Int J Stroke*. 2008;3:158–164. doi: 10.1111/j.1747-4949.2008.00204.x
563. Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, Rosand J. Association between blood pressure control and risk of

- recurrent intracerebral hemorrhage. *JAMA*. 2015;314:904–912. doi: 10.1001/jama.2015.10082
564. Charidimou A, Boulouis G, Xiong L, Jessel MJ, Roongpiboonsopit D, Ayres A, Schwab KM, Rosand J, Gurol ME, Greenberg SM, et al. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2017;88:1607–1614. doi: 10.1212/WNL.0000000000003866
565. Hanger HC, Wilkinson TJ, Fayed-Iskander N, Sainsbury R. The risk of recurrent stroke after intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 2007;78:836–840. doi: 10.1136/jnnp.2006.106500
566. Huhtakangas J, Löppönen P, Tetri S, Juvela S, Saloheimo P, Bode MK, Hillbom M. Predictors for recurrent primary intracerebral hemorrhage: a retrospective population-based study. *Stroke*. 2013;44:585–590. doi: 10.1161/STROKEAHA.112.671230
567. Inagawa T. Recurrent primary intracerebral hemorrhage in Izumo City, Japan. *Surg Neurol*. 2005;64:28–35. doi: 10.1016/j.surneu.2004.09.039
568. Leasure AC, King ZA, Torres-Lopez V, Murthy SB, Kamel H, Shoamanesh A, Al-Shahi Salman R, Rosand J, Ziai WC, Hanley DF, et al. Racial/ethnic disparities in the risk of intracerebral hemorrhage recurrence. *Neurology*. 2020;94:e314–e322. doi: 10.1212/WNL.0000000000008737
569. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014;85:660–667. doi: 10.1136/jnnp-2013-306476
570. Vermeer SE, Algra A, Franke CL, Koudstaal PJ, Rinkel GJ. Long-term prognosis after recovery from primary intracerebral hemorrhage. *Neurology*. 2002;59:205–209. doi: 10.1212/wnl.59.2.205
571. Weimar C, Benemann J, Terborg C, Walter U, Weber R, Diener HC; German Stroke Study Collaboration. Recurrent stroke after lobar and deep intracerebral hemorrhage: a hospital-based cohort study. *Cerebrovasc Dis*. 2011;32:283–288. doi: 10.1159/000330643
572. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, Smith EE, Greenberg MS, Rosand J, Viswanathan A. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2010;75:693–698. doi: 10.1212/WNL.0b013e3181ee40f
573. Miki K, Natori Y, Kai Y, Yamada T, Mori M, Noguchi N, Koga H. Absence of microbleeds reduces the risk for recurrent intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2020;29:104585. doi: 10.1016/j.jstrokecerebrovasdis.2019.104585
574. Perry LA, Rodrigues M, Al-Shahi Salman R, Samarasekera N. Incident cerebral microbleeds after intracerebral hemorrhage. *Stroke*. 2019;50:2227–2230. doi: 10.1161/STROKEAHA.118.023746
575. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. *Stroke*. 2004;35:1415–1420. doi: 10.1161/01.STR.0000126807.69758.0e
576. Charidimou A, Boulouis G, Roongpiboonsopit D, Xiong L, Pasi M, Schwab KM, Rosand J, Gurol ME, Greenberg SM, Viswanathan A. Cortical superficial siderosis and recurrent intracerebral hemorrhage risk in cerebral amyloid angiopathy: large prospective cohort and preliminary meta-analysis. *Int J Stroke*. 2019;14:723–733. doi: 10.1177/1747493019830065
577. Moulin S, Casolla B, Kuchcinski G, Boulouis G, Rossi C, Hénon H, Leys D, Cordonnier C. Cortical superficial siderosis: a prospective observational cohort study. *Neurology*. 2018;91:e132–e138. doi: 10.1212/WNL.0000000000005778
578. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, Ikeda D, Greenberg SM. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Engl J Med*. 2000;342:240–245. doi: 10.1056/NEJM20001273420403
579. Zia E, Engström G, Svensson PJ, Norrvig B, Pessah-Rasmussen H. Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. *Stroke*. 2009;40:3567–3573. doi: 10.1161/STROKEAHA.109.556324
580. Rodriguez-Torres A, Murphy M, Kourkoulis C, Schwab K, Ayres AM, Moomaw CJ, Young Kwon S, Berthaud JV, Gurol ME, Greenberg SM, et al. Hypertension and intracerebral hemorrhage recurrence among White, Black, and Hispanic individuals. *Neurology*. 2018;91:e37–e44. doi: 10.1212/WNL.0000000000005729
581. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, Davis S, Donnan G, MacMahon S, Neal B, et al; Writing Committee for the PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS trial. *Stroke*. 2004;35:116–121. doi: 10.1161/01.STR.0000106480.76217.6F
582. Hilkens NA, Greving JP, Algra A, Klijn CJ. Blood pressure levels and the risk of intracerebral hemorrhage after ischemic stroke. *Neurology*. 2017;88:177–181. doi: 10.1212/WNL.0000000000003489
583. Zahuranec DB, Wing JJ, Edwards DF, Menon RS, Fernandez SJ, Burgess RE, Sobotka IA, German L, Truth AJ, Shara NM, et al. Poor long-term blood pressure control after intracerebral hemorrhage. *Stroke*. 2012;43:2580–2585. doi: 10.1161/STROKEAHA.112.663047
584. Arima H, Tzourio C, Butcher K, Anderson C, Bousser MG, Lees KR, Reid JL, Omae T, Woodward M, MacMahon S, et al; PROGRESS Collaborative Group. Prior events predict cerebrovascular and coronary outcomes in the PROGRESS trial. *Stroke*. 2006;37:1497–1502. doi: 10.1161/01.STR.0000221212.36860.c9
585. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 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. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000665
586. Cho SM, Moazami N, Katz S, Starling R, Frontera JA. Reversal and resumption of antithrombotic therapy in LVAD-associated intracranial hemorrhage. *Ann Thorac Surg*. 2019;108:52–58. doi: 10.1016/j.athoracsur.2019.01.016
587. Kuramatsu JB, Sembill JA, Gerner ST, Sprügel MI, Hagen M, Roeder SS, Endres M, Haeusler KG, Sobesky J, Schurig J, et al. Management of therapeutic anticoagulation in patients with intracerebral hemorrhage and mechanical heart valves. *Eur Heart J*. 2018;39:1709–1723. doi: 10.1093/eurheartj/ehy056
588. Ding X, Liu X, Tan C, Yin M, Wang T, Liu Y, Mo L, Wei X, Tan X, Deng F, et al. Resumption of antiplatelet therapy in patients with primary intracranial hemorrhage—benefits and risks: a meta-analysis of cohort studies. *J Neurol Sci*. 2018;384:133–138. doi: 10.1016/j.jns.2017.11.009
589. RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet*. 2019;393:2613–2623. doi: 10.1016/S0140-6736(19)30840-2
590. Biffi A, Kuramatsu JB, Leasure AC, Kamel H, Kourkoulis C, Schwab K, Ayres AM, Elm J, Gurol ME, Greenberg SM, et al. Oral anticoagulation and functional outcome after intracerebral hemorrhage. *Ann Neurol*. 2017;82:755–765. doi: 10.1002/ana.25079
591. Chao TF, Liu CJ, Liao JN, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FF, et al. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. *Circulation*. 2016;133:1540–1547. doi: 10.1161/CIRCULATIONAHA.115.019794
592. Korompoki E, Filippidis FT, Nielsen PB, Del Giudice A, Lip GYH, Kuramatsu JB, Huttner HB, Fang J, Schulman S, Martí-Fàbregas J, et al. Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation. *Neurology*. 2017;89:687–696. doi: 10.1212/WNL.0000000000004235
593. Ottosen TP, Grijota M, Hansen ML, Brandes A, Damgaard D, Husted SE, Johnsen SP. Use of antithrombotic therapy and long-term clinical outcome among patients surviving intracerebral hemorrhage. *Stroke*. 2016;47:1837–1843. doi: 10.1161/STROKEAHA.116.012945
594. Park YA, Uhm JS, Pak HN, Lee MH, Joung B. Anticoagulation therapy in atrial fibrillation after intracranial hemorrhage. *Heart Rhythm*. 2016;13:1794–1802. doi: 10.1016/j.hrthm.2016.05.016
595. Poli L, Grassi M, Zedde M, Marcheselli S, Silvestrelli G, Sessa M, Zini A, Paciaroni M, Azzini C, Gamba M, et al; Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy) Investigators. Anticoagulants resumption after warfarin-related intracerebral haemorrhage: the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy). *Thromb Haemost*. 2018;118:572–580. doi: 10.1055/s-0038-1627454
596. Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke*. 2010;41:2860–2866. doi: 10.1161/STROKEAHA.110.593087
597. Pennert J, Overholser R, Asplund K, Carlberg B, Van Rompaye B, Wiklund PG, Eriksson M. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. *Stroke*. 2017;48:314–320. doi: 10.1161/STROKEAHA.116.014643
598. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, et al; PREVAIL and PROTECT AF Investigators. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol*. 2017;70:2964–2975. doi: 10.1016/j.jacc.2017.10.021
599. Holmes DR Jr, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. *J Am Coll Cardiol*. 2015;65:2614–2623. doi: 10.1016/j.jacc.2015.04.025





review and meta-analysis. *Lancet Public Health*. 2017;2:e108–e120. doi: 10.1016/S2468-2667(17)30003-8

636. English C, Healy GN, Olds T, Parfitt G, Borkoles E, Coates A, Kramer S, Bernhardt J. Reducing sitting time after stroke: a phase II safety and feasibility randomized controlled trial. *Arch Phys Med Rehabil*. 2016;97:273–280. doi: 10.1016/j.apmr.2015.10.094
637. Liljehult J, Christensen T, Molsted S, Overgaard D, Mesot Liljehult M, Møller T. Effect and efficacy of lifestyle interventions as secondary prevention. *Acta Neurol Scand*. 2020;142:299–313. doi: 10.1111/ane.13308
638. Minshall C, Pascoe MC, Thompson DR, Castle DJ, McCabe M, Chau JPC, Jenkins Z, Cameron J, Ski CF. Psychosocial interventions for stroke survivors, carers and survivor-carer dyads: a systematic review and meta-analysis. *Top Stroke Rehabil*. 2019;26:554–564. doi: 10.1080/10749357.2019.1625173
639. Vloothuis JD, Mulder M, Veerbeek JM, Konijnenbelt M, Visser-Meily JM, Ket JC, Kwakkel G, van Wegen EE. Caregiver-mediated exercises for improving outcomes after stroke. *Cochrane Database Syst Rev*. 2016;12:CD011058. doi: 10.1002/14651858.CD011058.pub2
640. Wang C, Redgrave J, Shafizadeh M, Majid A, Kilner K, Ali AN. Aerobic exercise interventions reduce blood pressure in patients after stroke or transient ischaemic attack: a systematic review and meta-analysis. *Br J Sports Med*. 2019;53:1515–1525. doi: 10.1136/bjsports-2017-098903
641. Lichtenstein AH, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, Rebholz CM, Sacks FM, Thorndike AN, Van Horn L, Wylie-Rosett; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; and Stroke Council. 2021 Dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e472–e487. doi: 10.1161/CIR.0000000000001031
642. Cheng HY, Chair SY, Chau JP. The effectiveness of psychosocial interventions for stroke family caregivers and stroke survivors: a systematic review and meta-analysis. *Patient Educ Couns*. 2014;95:30–44. doi: 10.1016/j.pec.2014.01.005
643. Walker MF, Birchall S, Cobley C, Condon L, Fisher R, Fletcher-Smith J, Golding-Day MR, Greensmith C, Kontou E, Matias O, et al. Biopsychosocial Intervention for Stroke Carers (BISC): results of a feasibility randomised controlled trial and nested qualitative interview study. *Clin Rehabil*. 2020;34:1268–1281. doi: 10.1177/0269215520937039
644. Akoudad S, Portegies ML, Koudstaal PJ, Hofman A, van der Lugt A, Ikram MA, Vernooij MW. Cerebral microbleeds are associated with an increased risk of stroke: the Rotterdam Study. *Circulation*. 2015;132:509–516. doi: 10.1161/CIRCULATIONAHA.115.016261
645. Charidimou A, Boulouis G, Xiong L, Pasi M, Roongpiboonsopit D, Ayres A, Schwab KM, Rosand J, Gurol ME, Viswanathan A, et al. Cortical superficial siderosis evolution. *Stroke*. 2019;50:954–962. doi: 10.1161/STROKEAHA.118.023368
646. Lee SH, Ryu WS, Roh JK. Cerebral microbleeds are a risk factor for warfarin-related intracerebral hemorrhage. *Neurology*. 2009;72:171–176. doi: 10.1212/01.wnl.0000339060.11702.dd
647. Lovelock CE, Cordonnier C, Naka H, Al-Shahi Salman R, Sudlow CL, Sorimachi T, Werring DJ, Gregoire SM, Imaizumi T, Lee SH, et al; Edinburgh Stroke Study Group. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. *Stroke*. 2010;41:1222–1228. doi: 10.1161/STROKEAHA.109.572594
648. Wilson D, Ambler G, Lee KJ, Lim JS, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, Hennerici M, et al; Microbleeds International Collaborative Network. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2019;18:653–665. doi: 10.1016/S1474-4422(19)30197-8
649. Best JG, Ambler G, Wilson D, Lee KJ, Lim JS, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, et al; Microbleeds International Collaborative Network. Development of imaging-based risk scores for prediction of intracranial haemorrhage and ischaemic stroke in patients taking anti-thrombotic therapy after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2021;20:294–303. doi: 10.1016/S1474-4422(21)00024-7NoneNone

# Stroke