CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

MANAGEMENT OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE

Seventh Edition - New Module 2020

Ashkan Shoamanesh (Co-chair), M. Patrice Lindsay, Lana A Castellucci, Anne Cayley, Mark Crowther, Kerstin de Wit, Shane W English, Sharon Hoosein, Thien Huynh, Michael Kelly, Cian J O'Kelly, Jeanne Teitelbaum, Samuel Yip, Dar Dowlatshahi, Eric E Smith, Norine Foley, Aleksandra Pikula, Anita Mountain, Gord Gubitz and Laura C. Gioia(Co-chair), on behalf of the Canadian Stroke Best Practices Advisory Committee in collaboration with the Canadian Stroke Consortium and the Canadian Hemorrhagic Stroke Trials Initiative Network (CoHESIVE).

October 2020

Heart&Stroke Foundation
Fondation des maladies du cœur et de l'AVC

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS
MANAGEMENT OF SPONTANEOUS INTRACERBRAL HEMORRHAGE SEVENTH EDITION, 2020

Table of Contents

PART ONE: CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS INTRODUCTION AND OVERVIEW

I. Introduction to the Canadian Stroke Best Practice Recommendations

The *Canadian Stroke Best Practice Recommendations* (*CSBPR*) are intended to provide up-to-date evidence-based guidelines for the prevention and management of stroke, and to promote optimal recovery and reintegration for people who have experienced stroke (patients, families and informal caregivers). The CSBPR are under the leadership of the Heart and Stroke Foundation, Canada.

The theme of the Seventh Edition of the *CSBPR* is building connections to optimize individual outcomes. People who have experienced a stroke often present to the healthcare system with multiple comorbid conditions – some that may contribute to their stroke, some that are consequences of their stroke, and some unrelated. One study revealed that approximately 80% of people who survive a stroke have on average five other conditions and a wide range of psychosocial issues (Nelson et al , 2016). These conditions must be considered as treatment and ongoing care planning is personalized and person-centred. In addition, there is strong evidence of the intrinsic connections between the heart and brain, and management of people following stroke should take heart health and possible association with vascular cognitive impairment into consideration. The healthcare system is often designed in siloes with different planning and organization for individual conditions, that are not integrated across conditions, even related vascular conditions. As people transition across settings and phases of care following a stroke, they report experiencing anxiety and feeling quite overwhelmed. Individualized care and ensuring connections are made within the community have a significant impact on short and long-term patient outcomes.

The Seventh Edition of the *CSBPR* includes a broader wholistic focus and take into consideration issues of multimorbidity and increasing complexity of people who experience stroke. In addition, a more purposeful review of sex and gender representation in the seminal clinical trials upon which the recommendations are based has been undertaken to determine the extent to which available evidence has included both male and female subjects in sufficient proportions to be able to detect outcomes and generalize to a broader population. These findings are presented in the discussion sections of the module and integrated into the actual recommendations where appropriate to do so. Accompanying performance measures have been expanded to include system indicators, clinical indicators and new patient reported outcome measures, supporting our wholistic focus.

The goal of disseminating and implementing these recommendations is to optimize evidence-based stroke care across Canada, reduce practice variations in the care of stroke patients, and narrow the gap between current knowledge and clinical practice.

This module on the management of people with intracerebral hemorrhage (ICH) is a new addition for the Seventh Edition of the *CSBPR*. Prior to this edition, ICH was included in the Acute Stroke Management module, and was limited to management in the first 12 hours, as much of the care associated with recovery following that time period would be similar to people with acute ischemic stroke. With the growing evidence on ICH, a separate module focused on this topic across the continuum is warranted.

These recommendations have been developed in collaboration with the Canadian Stroke Consortium.

II. Overview of Intracerebral Hemorrhage Module

In the *CSBPR* Seventh Edition, all recommendations related to ICH have been consolidated into one module that addresses ICH across the continuum. This enables health professionals to have one source for ICH treatment and management. This module includes emergency management of ICH, inpatient care, rehabilitation and secondary prevention. It focuses on recommendations for care that are unique to ICH and differ from ischemic stroke and TIA. This module contains updates and additions to previously existing recommendations on acute management of ICH in the emergency department (Section 1). All additional recommendations are new content additions to this module.

For initial prehospital management of a stroke patient, prior to confirmed diagnosis of ICH, the *CSBPR* Acute Stroke Management module, sections 1 to 4, apply and should be followed up until a diagnosis of ICH is confirmed, then these recommendations become the applicable set.

This module is developed in collaboration with the COHESIVE Network. CoHESIVE (www.phri.ca/cohesive/) is a Canada-centric international multidisciplinary network of over 50 investigators devoted to preventing ICH and bettering the lives of ICH survivors through collaborative research, education and patient advocacy.

III. Definitions:

Hemorrhagic stroke: A stroke caused by the rupture of a blood vessel within the brain tissue, subarachnoid space or intraventricular space.

Intracranial hemorrhage includes bleeding within the cranial vault and encompasses intraventricular, intraparenchymal, subarachnoid, subdural and epidural hemorrhage.

Spontaneous, nontraumatic intracerebral hemorrhage is bleeding within the brain parenchyma without obvious systemic, neoplastic, traumatic, or macrovascular etiology. This stroke subtype accounts for about 10-15%[a] of all strokes and a disproportionately higher number of stroke related deaths. ICH are often categorized according to their location within the brain: lobar, deep, cerebellar, and brainstem.

Hemorrhagic infarct: Hemorrhagic infarct is defined as a hemorrhagic transformation into an area of arterial ischemic infarction or venous thrombosis associated tissue congestion.

IV. Guideline Development Methodology

The *CSBPR* present high-quality, evidence-based stroke care guidelines in a standardized framework to support healthcare professionals across all disciplines. Implementation of these recommendations is expected to reduce practice variations and close the gaps between evidence and practice.

The recommendations are targeted to health professionals throughout the health system who care for those affected by stroke. Health system policy makers, planners, funders, senior managers, and administrators who are responsible for the coordination and delivery of stroke services within a province or region will also find this document relevant and applicable to their work.

The methodology for updating the recommendations includes 14 distinct steps to ensure a thorough and rigorous process. These include the following (details available online):

1. Establish an expert interprofessional writing group representing relevant disciplines across the continuum of care and range of settings (Appendix One);
2. Establish Community Consultation and Review Panel comprised of people with lived experience, including people with stroke, caregivers and family members;
3. Systematic search, appraisal and update of research literature up to May 2019;
4. Systematic search and appraisal of external reference guideline recommendations;
5. Create and or update of evidence summary tables;

[a] based on 2017-18 admission rates to hospitals in Canada, Canadian Institute for Health Information

6. Writing group review and revision of existing recommendations, development of new recommendations as required, adhering to all elements defined within the Agree 2 criteria where appropriate. Please see https://www.agreetrust.org/resource-centre/agree-ii/ for more information.
7. Writing group review and revision of existing recommendations, development of new recommendations as required, then final voting to achieve consensus;
8. Submission of proposed module update to the;
9. Internal review of proposed module update by the Canadian Stroke Best Practice and Quality Advisory Committee.
10. External review by leading experts in Canada and internationally, and final edits as required (Appendix One);
11. Update of educational materials and implementation resources;
12. Final approvals, endorsement and translation of chapter;
13. Publication, public release and dissemination of final module update;
14. Continue with ongoing review and update process.

The detailed methodology and explanations for each of these steps in the development and dissemination of the *CSBPR* is available in the *Canadian Stroke Best Practice Recommendations Overview and Methodology* manual available on the Canadian stroke best practices website at https://www.strokebestpractices.ca/recommendations/overview-methods-and-knowledge-exchange

Management of Conflicts of Interest within CSBPR: All potential participants in the recommendation development and review process are required to sign confidentiality agreements and to declare all actual and potential conflicts of interest in writing prior to participation. Any conflicts of interest that are declared are reviewed by the Chairs of the CSBPR Advisory Committee and appropriate Heart & Stroke staff members for their potential impact. Potential members of any writing group who have conflicts that are considered to be significant with respect to the topics within the module of interest are not selected for writing group or reviewer roles. Participants who have conflicts for one particular topic area are identified at the beginning of discussions for that topic and are recused from voting. If the persons in conflict are one of the cochairs then they are recused from chair responsibilities for that discussion, and another non-conflicted participant assumes the chair role for that discussion and voting to ensure balanced and unbiased discussions. Heart & Stroke senior staff members, who do not have any conflicts of interest, participate in all writing group discussions and will intervene if there is any perceived untoward bias by a writing group member. Declarations of Conflict of interest for writing group members can be found in Appendix One.

Assigning Evidence Levels: The writing group was provided with comprehensive evidence tables that include summaries of all high-quality evidence identified through the literature searches. The writing group discusses and debates the value of the evidence and through consensus develops a final set of proposed recommendations. Through their discussions, additional research may be identified and added to the evidence tables if consensus on the value of the research is achieved. All recommendations are assigned a level of evidence ranging from A to C, according to the criteria defined in Table 1. When developing and including “C-Level” recommendations, consensus is obtained among the writing group and validated through the internal and external review process. This level of evidence is used cautiously, and only when there is a lack of stronger evidence for topics considered important system drivers for stroke care (e.g., transport using ambulance services or some screening practices). An additional category for Clinical Considerations has been added for the Sixth Edition. Included in this section are expert opinion statements in response to reasonable requests from a range of healthcare professionals who seek guidance and direction from the experts on specific clinical issues faced on a regular basis in the absence of any evidence on that topic.

Table 1: Summary of Criteria for Levels of Evidence Reported in the *Canadian Stroke Best Practice Recommendations* (Seventh Edition):

Level of Evidence	Criteria*
A	Evidence from a meta-analysis of randomized controlled trials or consistent findings from two or more randomized controlled trials. Desirable effects clearly outweigh undesirable effects or vice versa.
B	Evidence from a single randomized controlled trial or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies. Meta-analysis of non-randomized and/or observational studies. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa.
C	Writing group consensus on topics supported by limited research evidence. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa, as determined by writing group consensus.
Clinical Consideration	Reasonable practical advice provided by consensus of the writing group on specific clinical issues that are common and/or controversial and lack research evidence to guide practice.

* (adapted from Guyatt et al. 2008) [12]

Acknowledgements

Heart &Stroke gratefully acknowledges the *Management of Spontaneous Intracerebral Hemorrhage* writing group leaders and members all of whom have volunteered their time and expertise to the update of these recommendations. Members of the Canadian Stroke Consortium were involved in all aspects of the development of these recommendations. These recommendations underwent external review by: Aleksandra Pikula, Rustam Al-Shahi Salman, Steven Greenberg, Lisa Groulx, Carlos S Kase, Jeffrey Perry, Madgy Selim, Samuel Shulman, Judy Sherman, Sean Sopher, Catherine Varner, and Wendy Zai. We thank the Canadian Stroke Best Practices Advisory Committee members, including Eric Smith, Anita Mountain, Leanne Casaubon, Gord Gubitz, Dar Dowlatshahi, Dylan Blacquiere, Thalia Field, Farrell Leibovitch, Christine Papoushek, Jeffrey Habert, Barbara Campbell, Joyce Fung, Michael Hill, Tim Hillier, Thomas Jeerakathil, Eddy Lang, Pascale Lavoie, Beth Linkewich, Colleen O'Connell, Melanie Penn, Jai Shankar, Debbie Timpson, Theodore Wein, and Katie White. We acknowledge and thank Norine Foley and the evidence analysis team at workHORSE; Laurie Charest, Andrea de Jong, Kirsten Eldridge and Rebecca McGuff of Heart & Stroke for coordination of the *CSBPR* teams and processes; and the Heart & Stroke Communications and Digital internal teams who contributed to the development of these recommendations and publication.

Funding

The development of the *CSBPR* is funded in its entirety by Heart & Stroke. No funds for the development of these guidelines come from commercial interests, including pharmaceutical and device companies. All members of the recommendation writing groups and external reviewers are volunteers and do not receive any remuneration for participation in guideline development, updates and reviews. All participants complete a conflict of interest declaration prior to participation.

Citing the Management of Intracerebral Hemorrhage 2020 Module

Ashkan Shoamanesh, M. Patrice Lindsay, Lana A Castellucci, Anne Cayley, Mark Crowther, Kerstin de Wit, Shane W English, Sharon Hoosein, Thien Huynh, Michael Kelly, Cian J O'Kelly, Jeanne Teitelbaum, Samuel Yip, Dar Dowlatshahi, Eric E Smith, Norine Foley, Aleksandra Pikula, Anita Mountain, Gord Gubitz and Laura C. Gioia, on behalf of the Canadian Stroke Best Practices and Quality Advisory Committee in collaboration with the Canadian Stroke Consortium and the CoHESIVE Network. Canadian Stroke Best Practice Recommendations: Management of Intracerebral Hemorrhage, Seventh Edition, 2020; Toronto, Ontario Canada: Heart and Stroke Foundation.

The recommendations included in this module are also published in the International Journal of Stroke:

Shoamanesh (Co-chair), A., Patrice Lindsay, M., Castellucci, L. A., Cayley, A., Crowther, M., de Wit, K., English, S. W., Hoosein, S., Huynh, T., Kelly, M., O'Kelly, C. J., Teitelbaum, J., Yip, S., Dowlatshahi, D., Smith, E. E., Foley, N., Pikula, A., Mountain, A., Gubitz, G., & Gioia, L. C. (2020). Canadian stroke best practice recommendations: Management of Spontaneous Intracerebral Hemorrhage, 7th Edition Update 2020. International Journal of Stroke. https://doi.org/10.1177/1747493020968424

English Link: https://doi.org/10.1177/1747493020968424

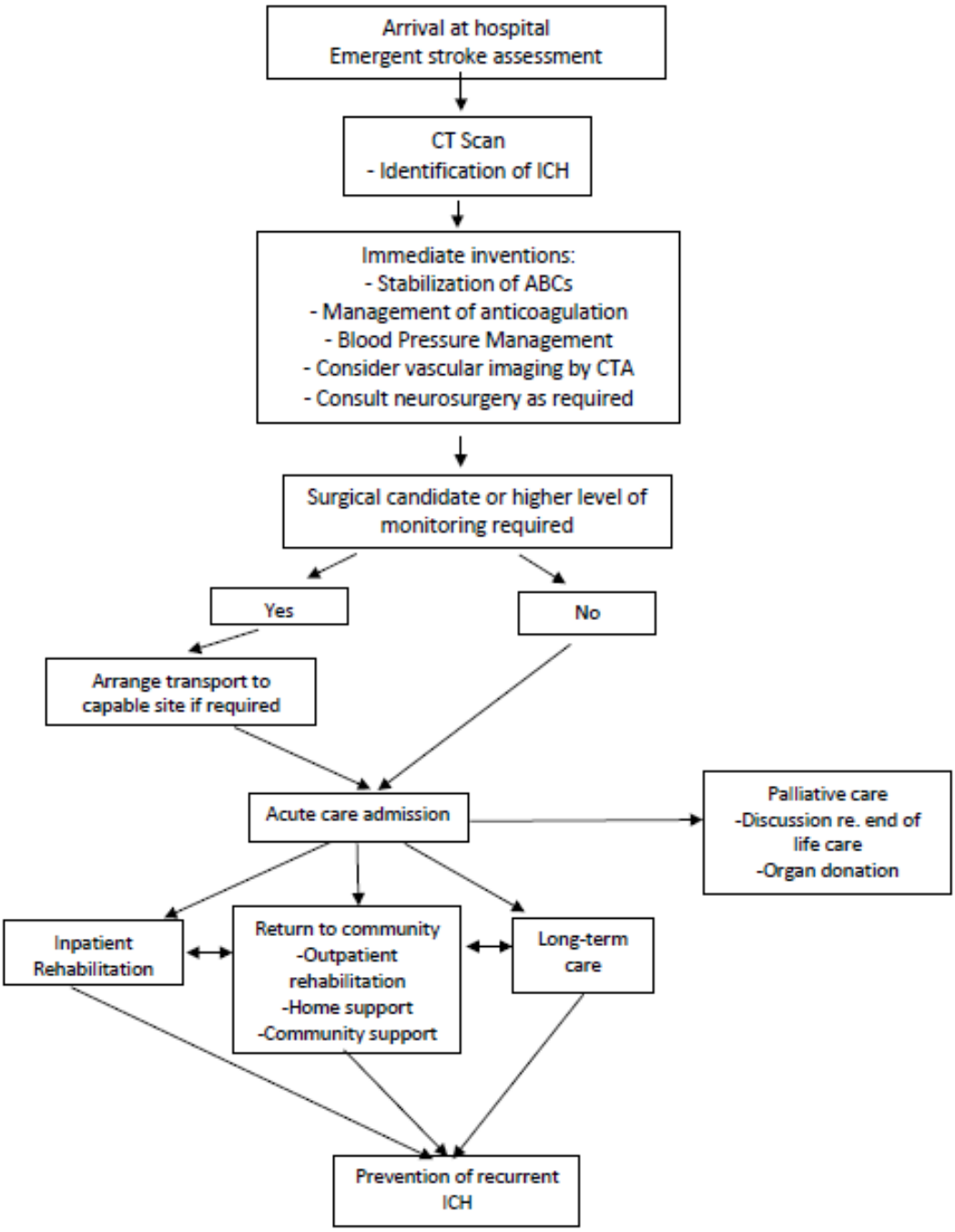
French Link:

https://journals.sagepub.com/doi/suppl/10.1177/1747493020968424/suppl_file/sj-pdf-1-wso-10.1177_1747493020968424.pdf

Comments

We invite comments, suggestions, and inquiries on the development and application of the *CSBPR.* Please forward comments to the Stroke Team at Heart & Stroke: strokebestpractices@heartandstroke.ca.

Figure One: Intracerebral Hemorrhage Patient Flow Map



Part Two: *Canadian Stroke Best Practice Recommendations* Spontaneous Intracerebral Hemorrhage

Section One: Emergency Management of Intracerebral Hemorrhage

NOTES on these recommendations:

- *These recommendations provide guidance in the management of spontaneous intracerebral hemorrhage (ICH), not hemorrhagic conversion of an ischemic infarction.*
- *These recommendations may not be applicable to ICH of secondary causes*
- *These recommendations should be referred to once a confirmed diagnosis of ICH has been established following brain imaging.*
- *Prior to diagnosis of ICH, follow the Initial assessments and imaging guidelines defined in the CSBPR Acute Stroke Management module 2018 (Sections 2, 3, 4) for all patients who arrive at hospital with a suspected stroke and during prehospital management.*

Recommendations

1.0 Intracerebral hemorrhage should be treated as a medical emergency. When intracerebral hemorrhage is suspected (or confirmed), patients should be evaluated urgently [Evidence Level B] by physicians with expertise in acute stroke management [Evidence Level C].

Note: For patients presenting in community or rural hospitals, Telestroke modalities could facilitate rapid access to stroke expertise for consultation and decision-making regarding transfer to a higher level of care.

1.1 Initial Clinical Assessment of Intracerebral Hemorrhage

i. A severity score based on neurological exam findings should be conducted as part of the initial assessment [Evidence Level B]. The National Institute of Health Stroke Score (NIHSS) is preferred for awake or drowsy patients, or a Glasgow Coma Scale (GCS) in patients who are obtunded, semi or fully comatose [Evidence Level C]. *Note, the GCS has been found to be a strong predictor of outcomes following ICH.*

   a. Patients with declining GCS and/or equal to less than 8 should be rapidly assessed for airway support by endotracheal intubation [Evidence Level B].

   b. Patients with reduced level of consciousness, pupillary changes and/or other signs of herniation should have temporizing maneuvers to manage presumed elevation in intracranial pressure (ICP), such as temporary hyperventilation and hyperosmotics (e.g. mannitol or 3% saline) [Evidence Level C].

ii. Patients with suspected ICH should undergo computerized tomography (CT) immediately following stabilization to confirm diagnosis, location and extent of hemorrhage [Evidence Level A]. *Refer to CSBPR Acute Stroke Management module for additional information on initial brain imaging.*

iii. In patients with confirmed acute ICH, intracranial vascular imaging is recommended for most patients to exclude an underlying lesion such as an aneurysm or arteriovenous malformation or cerebral sinus venous thrombosis [Evidence Level B].

   a. Factors that increase the yield of angiography include age <50 years, female sex, lobar or infratentorial location of ICH, accompanying intraventricular hemorrhage, absence of neuroimaging markers of cerebral small vessel disease and/or absence of hypertension or impaired coagulation [Evidence Level B].

   b. Where suspicion is high for an underlying vascular lesion, the vascular imaging should

be performed at the same time as brain imaging [Evidence Level C].

iv. Evaluation of patients with acute ICH should include questions about medication history [Evidence Level C], and antithrombotic therapy, measurement of platelet count, partial thromboplastin time (PTT) and International Normalized Ratio (INR) [Evidence Level A].

v. Patients should be assessed for clinical signs of increased ICP such as pupil reaction and level of consciousness [Evidence Level B].

vi. A GCS score and neurovital signs should be conducted at baseline and repeated at least hourly for the first 24 hours, depending on stability of patient. [Evidence Level C].

vii. If physicians with expertise in acute stroke management are not available onsite, protocols should be in place to contact appropriate experts through virtual telestroke technology [Evidence Level B] to expedite patient assessment and decisions regarding transport to a higher level of care [Evidence Level C].

Clinical considerations for Section 1.1

i. The resolution of CT angiography is preferred over MR angiography when screening for underlying vascular anomalies.

ii. Clinical signs of increased ICP include reduced level of consciousness, dilated unresponsive pupils, new cranial nerve VI palsies or other false localizing neurological signs, worsening headache and/or nausea/vomiting, and elevated blood pressure with reduced heart rate and irregular/ decreased respirations (Cushing's reflex).

iii. Potential unstable patients requiring greater monitoring frequency (i.e. neurovital signs hourly for first 24 hours) include patients with large (>30 cc) ICH volume, depressed or declining GCS (<12), worsening neurological disability, infratentorial location, associated intraventricular hemorrhage or hydrocephalus, refractory hypertension, and/or neuroimaging markers of ICH expansion (see section 1.5).

iv. The use of tranexamic acid has been shown to be safe in a large phase 3 trial (TICH-2) but there was no effect on the primary outcome of functional status at 90 days. Post-hoc pre-specified subgroup analyses showed better functional status in patients with baseline systolic blood pressure less than 170 mm Hg. However, this post-hoc finding has yet to be confirmed. Overall, the clinical role of tranexamic acid for spontaneous ICH remains unclear and there is no evidence for its use in the setting of anticoagulant-related ICH.

1.2 Blood Pressure Management

i. Blood pressure should be assessed on initial arrival to the Emergency Department and every 15 minutes thereafter until desired blood pressure target is achieved and maintained for the first 24 hours [Evidence Level C].

ii. Systolic blood pressure lowering to a target of < 140 mmHg systolic does not worsen neurological outcomes (relative to a target of 180 mmHg systolic) [Evidence level A]; however, clinical benefit has yet to be established [Evidence level A].

iii. Subsequent blood pressure monitoring should be tailored to the individual patients according to stability of the vital signs and intracranial pressure (ICP) [Evidence Level C].

iv. There is a lack of strong evidence to guide choice of initial blood pressure lowering agents.

Clinical Consideration for Section 1.2:

i. A systolic blood pressure threshold at an individual target of less than 140-160 mm Hg for the first 24-48 hours post ICH may be reasonable.

a. Factors that may favour a lower target within this range (i.e., < 140 mm HG) may include: presentation within 6 hours of symptom onset; presenting systolic blood pressure no greater than 220 mmHg; anticoagulation therapy; presence of neuroimaging markers of expansion (see section 1.5) and/or normal renal function.

ii. Parenteral labetalol, hydralazine, nicardapine and/or enalipril (oral or intravenous) may be considered for acute blood pressure reduction.

1.3 Management of Anticoagulation

i. Patients presenting with anticoagulant-related ICH should have their anticoagulation withheld and should be considered for immediate reversal, irrespective of the underlying indication for anticoagulation [Evidence Level B].

ii. Beyond initial investigations, further management should be tailored to the specific antithrombotic agent used [Evidence Level C].

iii. Warfarin should be reversed immediately with prothrombin complex concentrate (PCC) dosed as per local protocols and in conjunction with intravenous Vitamin K 10 mg [Evidence Level B].

iv. For patients on Direct oral anticoagulants (DOACs), most information about anticoagulation activity would come from establishing time of last dose, creatinine clearance, anti- Factor Xa level if available [Evidence Level C]; *Note: reversal should not be delayed while waiting for laboratory results, rather it should be based on clinical history*.

v. Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) should be stopped immediately and PCC administered at a dose of 50 units per Kg with a *maximum* dose of 3000 u [Evidence Level C]. *Note: There are no targeted anti-Factor Xa reversal agents available in Canada at this time.*

vi. Dabigatran should be stopped immediately and reversed with idarucizumab; patients should be given a total dose of 5 g, in 2 intravenous bolus doses of 2.5 g each, given no more than 15 minutes apart [Evidence Level B]. *Note: the doses should be given successively. There is no requirement for time delay between doses.*

a. If idarucizumab is not available, use of FEIBA (Anti-Inhibitor Coagulant Complex; activated PCC) is recommended at 50 units per Kg to a maximum of 2000 u [Evidence Level C];

b. If both agents are not available consider, four-factor PCC at a dose of 50 units per Kg to a *maximum* dose of 3000 units [Evidence Level C].

vii. If the patient has received therapeutic low molecular weight heparin (LMWH) within the past 12 hours, consider administering protamine [Evidence Level C].

viii. If the patient is receiving intravenous heparin infusion at the time of ICH, infusion should be immediately discontinued, and consider administering protamine [Evidence Level C].

ix. Antiplatelet agents (e.g. acetylsalicylic acid (ASA), clopidogrel, dipyridamole/ASA, ticagrelor) should be stopped immediately [Evidence Level C].

x. Platelet transfusions are not recommended (in the absence of significant thrombocytopenia) and may be harmful [Evidence Level B]

Clinical Considerations for Section 1.3

i. Dilute thrombin time can be used as a surrogate measure of anticoagulation in patients on dabigatran; however, we advise against delaying reversal to obtain these results.

ii. Andexanet alfa is not yet commercially available in Canada but has been shown to reverse the anticoagulant effect of Factor Xa inhibitors in a non-randomized single-arm clinical trial. It could be considered once commercially available.

1.4 Consultation with Neurosurgery

i. Neurosurgical consultation can be considered as a life-saving intervention for large ICH that is surgical accessible or causing obstructive hydrocephalus. Smaller non-life-threatening ICH require stroke unit care and do not necessarily require neurosurgical consultation [Evidence Level C].

Note: *If neurosurgical services not available onsite, initial consultation should be initiated with nearest neurosurgical services without delay, using telephone or Telemedicine technology.*

Clinical Consideration for Section 1.4:

i. Participation and enrollment in randomized trials should be considered where possible.

1.5 Neuro-imaging

Note: *For recommendations on initial neuro-imaging of all suspected acute stroke patients upon initial arrival to hospital refer to CSBPR Acute Stroke Management module, Section 3 and this module Section 1.1 (ii – iii). And Acute Stroke Management during Pregnancy module.*

1.5.1 Recommended additional urgent neuroimaging to confirm ICH diagnosis

i. In cases where CTA is not obtained as part of the initial acute stroke protocol, non-invasive angiography (CTA or gadolinium enhanced MRA) of the intracranial circulation should be considered and, if proceeding, be performed promptly on most patients presenting with ICH to identify potential underlying vascular lesions or spot sign/extravasation [Evidence Level B].

   a. If suspected, CT venography can be performed to evaluate for cerebral venous sinus thrombosis [Evidence Level B].

Clinical Considerations for Section 1.5.1

i. Hemorrhage volume (cc) can be quickly estimated using the formula ABC/2 where A is the greatest hemorrhage diameter in cm on an axial slice, B is the largest diameter perpendicular to A, and C is the approximate number of CT slices with hemorrhage multiplied by the slice thickness in cm (i.e. 5 mm slice thickness = 0.5).

ii. Urgent repeat CT should be performed in patients when there is clinical deterioration or worsening level of consciousness. A repeat CT at 24 hours may be considered even in the absence of clinical deterioration to document hematoma expansion (occurring in ~30% of acute ICH) and to identify extent of mass effect, new intraventricular hemorrhage, or evolution of hydrocephalus

iii. Baseline clinical and imaging factors that are predictive of hematoma expansion and ensuing worse outcomes include short time from symptom onset to baseline imaging (i.e. 6 hours), larger hematoma volume and antithrombotic therapy. Additional imaging predictors of hematoma expansion including heterogeneous hematoma density or regions of intra-hematomal hypodensity, irregular hematoma shape and satellite hematomas, amongst others, on non-contrast CT, as well as intra-hematomal contrast extravasation (Spot Sign) on CTA. However, these markers have yet to be proven useful for clinical interventions.

iv. Early marked vasogenic edema that is out of proportion to presumed timing of ICH may be suggestive of underlying hemorrhagic infarction, hemorrhagic tumor or cerebral venous sinus thrombosis. CT hyper-attenuation within a major dural venous sinus or cortical vein draining region of ICH is suggestive of cerebral venous sinus thrombosis

1.5.2 Recommended additional etiological neuroimaging

i. MRI should be considered to evaluate potential underlying mass lesions, hemorrhagic transformation of an ischemic infarct, and cavernous malformations [Evidence Level B].

   a. MRI can additionally provide information on microangiopathic changes to support the diagnosis of spontaneous ICH from underlying cerebral small vessel disease due to chronic hypertension and/or cerebral amyloid angiopathy [Evidence Level B].

   b. The optimal timing of initial MRI is uncertain [Evidence Level C].

ii. MRI with MR venogram and GRE/SWI may be considered to exclude cerebral venous thrombosis [Evidence Level B].

iii. Digital subtraction angiography (DSA) should be considered in select cases where there exists continued high suspicion of underlying vascular anomaly despite normal CTA and MRI, or non-invasive studies are suggestive of an underlying lesion [Evidence Level B].

   a. The yield of angiography is higher in the presence of the following clinical and radiologic predictors: younger age < 50 years, female sex, lobar/superficial or infratentorial location of ICH, associated intraventricular hemorrhage or subarachnoid hemorrhage, absence of prior history of hypertension or impaired coagulation, associated enlarged vessels or calcifications along the margin of the ICH, and absence of neuroimaging markers of cerebral small vessel disease [Evidence Level B].

iv. Where sufficient suspicion persists for an underlying lesion responsible for the index ICH, delayed repeat imaging with MRI and DSA following hematoma resolution (usually 3 months post ICH) can be used to detect an underlying lesion that may have initially been unidentified, such as tumors, cavernous malformations or small vascular anomalies initially compressed or obscured by the hematoma [Evidence Level B].

Clinical Considerations for Section 1.5:

i. The most prevalent cerebral small vessel diseases that contribute to spontaneous ICH are hypertensive arteriopathy and/or cerebral amyloid angiopathy (CAA). CT markers associated with these underlying microangiopathies include multiple chronic lacunes and brainstem, deep grey, periventricular and subcortical white matter disease. Similar findings can be seen on MRI, with addition of enlarged perivascular spaces on T2-weighted imaging, and cerebral microbleeds or cortical superficial siderosis on blood sensitive sequences (T2*-GRE and/or SWI). A strictly cortical/subcortical white matter distribution of these lesions, but with sparing of the brainstem and deep grey matter in older (≥55 years) patients with lobar or cerebellar ICH would favor CAA over hypertensive arteriopathy.

ii. The increased use of acute/subacute MRI has identified remote punctate DWI hyperintense lesions in up to 25% of spontaneous ICH patients. The underlying etiology of such lesions is currently under investigation, but seems to be strongly associated with the degree of underlying microangiopathy. An embolic workup could however still be considered in such cases, until their clinical significance becomes further elucidated.

1.6 Surgical management of ICH

i. External ventricular drainage (EVD) should be considered in patients with a reduced level of consciousness and hydrocephalus due to either intraventricular hemorrhage or mass effect [Evidence Level B].

ii. Surgical evacuation is not recommended if symptoms are stable and there are no signs of herniation [Evidence Level B]

   a. Intraventricular thrombolysis to treat spontaneous intraventricular hemorrhage with or without associated ICH is generally not recommended [Evidence Level B]. Treatment may reduce the risk of death but does not increase the chances of survival without major disability [Evidence Level B].

iii. Acute surgical intervention may be considered in patients with surgically accessible supratentorial hemorrhages and clinical signs of herniation (e.g., decreasing levels of consciousness (LOC), pupillary changes) [Evidence Level C], particularly in the following subgroups:

   a. Young patients (<65 years of age)

   b. Superficial ICH location (less than or equal to 1 cm from the cortical surface)

   c. Associated vascular or neoplastic lesion

iv. Patients with cerebellar hemorrhage may be considered for neurosurgical consultation, particularly in the setting of altered level of consciousness (LOC), new brainstem symptoms, or diameter of 3 or more cm [Evidence Level C].

   a. EVD placement should occur in conjunction with hematoma evacuation in the setting of concurrent hydrocephalus [Evidence Level C].

v. The clinical benefit of minimally invasive clot evacuation is yet to be established.

   a. Routine use of stereotactic thrombolysis and drainage (MISTIE technique (tPA)) is not recommended based on current evidence [Evidence Level B].

Clinical Considerations for Section 1.6:

i. Patients with significant hydrocephalus and normal level of consciousness should be monitored closely and could be considered for EVD at earliest signs of decreasing LOC.

ii. Intraventricular thrombolysis to treat spontaneous intraventricular hemorrhage with or without associated ICH may reduce the risk of death, but seems to increase the chances of survival with major disability.

iii. Based on the findings of one RCT (MISTIE III), stereotactic thrombolysis appears to be safe and reduces mortality compared to medical management alone, but does not improve functional outcomes. Successful hematoma volume reduction to < 15mL may be associated with functional outcome benefit.

iv. Endoscopic evacuation of deep and superficial ICH also decreases hematoma volume. Small randomized and non-randomized series have suggested benefit. The impact on functional outcomes is currently under assessment in larger randomized clinical trials.

v. Endoscopic evacuation without the use of thrombolysis is under ongoing investigations. Its routine use is not recommended outside the framework of a clinical trial.

vi. Confirmation of anticoagulation reversal should be obtained intraoperatively.

vii. Pneumatic compression devices (PCDs) should be placed preoperatively and maintained post operatively until pharmacologic DVT prophylaxis can be initiated.

Box One: Symptoms of Intracerebral Hemorrhage

Clinical assessment cannot reliably distinguish intracerebral hemorrhage from ischemic stroke; brain imaging is required. More frequent symptoms of ICH may include:

- Alteration in level of consciousness (present in approximately 50% of patients)
- Nausea and vomiting (approximately 40-50%)
- Sudden, severe headache (approximately 40%)
- Seizures (approximately 6-7%)
- Sudden weakness or paralysis of the face, arm or leg, or numbness, particularly on one side of the body
- Sudden vision changes
- Loss of balance or coordination
- Difficulty understanding, speaking (slurring, confusion), reading, or writing

Presentation:

- The classic presentation of ICH is sudden onset of a focal neurological deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness, and elevated blood pressure.
- Patients may present with symptoms upon awakening from sleep. Neurologic deficits are related to the site of parenchymal hemorrhage.
- Thus, ataxia is the initial deficit noted in cerebellar hemorrhage, whereas weakness may be the initial symptom with a basal ganglia hemorrhage.
- Early progression of neurologic deficits and decreased level of consciousness can be expected in 50% of patients with ICH. (Ramandeep Sahni and Jesse Weinberger; Vasc Health Risk Manag. 2007 October; 3(5): 701–709.)

Box Two: **Modified Boston Criteria (Linn 2010) ***

Table 1 **Classic and modified Boston criteria for CAA-related hemorrhage**

	Classic Boston criteria[2]	Modified Boston criteria
Definite CAA	Full postmortem examination demonstrating:	No modification[a]
	• Lobar, cortical, or corticosubcortical hemorrhage	
	• Severe CAA with vasculopathy	
	• Absence of other diagnostic lesion	
Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:	No modification[a]
	• Lobar, cortical, or corticosubcortical hemorrhage	
	• Some degree of CAA in specimen	
	• Absence of other diagnostic lesion	
Probable CAA	Clinical data and MRI or CT demonstrating:	Clinical data and MRI or CT demonstrating:
	• Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)	• Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or
	• Age ≥55 y	• Single lobar, cortical, or corticosubcortical hemorrhage and focal[b] or disseminated[c] superficial siderosis
	• Absence of other cause of hemorrhage	• Age ≥55 y
		• Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating:	Clinical data and MRI or CT demonstrating:
	• Single lobar, cortical, or corticosubcortical hemorrhage	• Single lobar, cortical, or corticosubcortical hemorrhage or
	• Age ≥55 y	• Focal[b] or disseminated[c] superficial siderosis
	• Absence of other cause of hemorrhage	• Age ≥55 y
		• Absence of other cause of hemorrhage or superficial siderosis

Abbreviation: CAA = cerebral amyloid angiopathy.
[a]No modification compared to the classic Boston criteria.
[b]Siderosis restricted to 3 or fewer sulci.
[c]Siderosis affecting at least 4 sulci.

* J. Linn, MD, A. Halpin, MD, P. Demaerel, PhD, J. Ruhland, A.D. Giese, PhD, M. Dichgans, PhD, M.A. van Buchem, PhD, H. Bruckmann, PhD, and S.M. Greenberg, PhD. **Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy.** Neurology. 2010 Apr 27; 74(17): 1346–1350. Doi: 10.1212/WNL.0b013e3181dad605

Rationale

The incidence of ICH is approximately 20/100,000 in the western populations (van Asch et al. 2010), with a cumulative risk of recurrence of 1% to 7% per year (Poon et al. 2014). The patients who present to hospital with suspected ICH often also have significant physiological abnormalities and comorbidities, which can complicate management. Medical conditions such as hypertension or the presence of a coagulopathy, may have an impact on treatment decisions. An efficient and focused assessment is required to understand the needs of each patient. Rapid identification, diagnosis and management by an expert stroke team are essential to reduce mortality, prevent complications and promote optimal recovery. Specialized care for people with ICH, especially neurosurgical care, is available at a limited number of larger community hospitals and tertiary centres, and people experiencing ICH outside of urban centres encounter longer delays in access to emergent assessment and intervention.

System Implications

1. Establishing multidisciplinary pathways for risk-benefit assessment of urgent management decisions in ICH patients.

2. Agreements to ensure patients initially managed in rural hospitals without neurovascular imaging capability have timely access to receive imaging.
3. Education for Emergency Medical Services, Emergency Department, and hospital staff on the characteristics and urgency for management of ICH patients.
4. Considerations should be given to northern, rural, remote and Indigenous residents to ensure immediate access to appropriate diagnostics and treatment is not delayed.
5. Protocols and standing orders to guide initial blood work and other clinical investigations.
6. Local protocols, especially in rural and remote locations, for rapid access to clinicians experienced in interpretation of diagnostic imaging, including access through telemedicine technology.
7. Provinces and regions should ensure availability of physicians and other healthcare professionals with stroke expertise, including recruitment and retention strategies to increase accessibility of acute stroke services for all Canadians.

Performance Measures

System Level:

1. Proportion of ICH patients treated in a primary or comprehensive stroke centre (H&S Level 4 or 5 stroke centre).
2. Proportion of ICH patients who bypass a smaller stroke-enabled hospital for direct transfer to a comprehensive stroke centre (H&S Level 4 or 5 stroke centre).
3. Proportion of ICH patients who arrive by ambulance.

Clinical Measures

4. Proportion of intracerebral hemorrhage patients who receive a CT or MRI within 25 minutes and one hour of hospital arrival.
5. Proportion of intracerebral hemorrhage patients who require surgical intervention.
6. Proportion of intracerebral hemorrhage patients who experience intraoperative complications and mortality during surgery for intracerebral hemorrhage.
7. Risk-adjusted mortality rates for intracerebral hemorrhage in-hospital, 30-day and one year.

Patient-Oriented Outcomes:

8. Distribution of functional ability measured by standardized functional outcome tools at time of discharge from hospital.
9. Self-reported quality of life following ICH at time of discharge from hospital, measured by a validated tool.
10. Family and caregiver ratings on the palliative care experience following the death in hospital of a patient with ICH.

Measurement Notes:

i. Mortality rates should be risk-adjusted for age, gender, stroke severity and comorbidities
ii. Time interval measurements should start from symptom onset of known or from triage time in the emergency department as appropriate.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- CoHESIVE: http://www2.phri.ca/cohesive/
- Stroke Engine: http://strokengine.ca/
- CSBPR Virtual Healthcare Toolkit: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/csbpr7-virtualcaretools-13may2020

- American College of Chest Physicians (ACCP) Anticoagulation Guidelines: http://www.chestnet.org/Guidelines-and-Resources
- Hypertension Canada Treatment Guidelines: https://guidelines.hypertension.ca/
- Canadian Stroke Best Practices Acute Stroke Management Table 2B: Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack:
- Canadian Stroke Best Practices Acute Stroke Management Appendix Three: Screening and Assessment Tools for Acute Stroke Severity

Information for People with Stroke, their Families and Caregivers

- Signs of stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- Stroke information: http://www.heartandstroke.ca/stroke/what-is-stroke
- Stroke Engine: http://strokengine.ca/
- Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Your Stroke Journey: A Guide for People Living with Stroke https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Stroke in young adults: A resource for patients and families: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final.ashx?rev=7338abd3dba746dc96180a057e244ce9
- Antiplatelet medications: https://www.heartandstroke.ca/heart-disease/treatments/medications/antiplatelet-medications

Summary of the Evidence 2020

Initial assessment

Patients with suspected intracerebral hemorrhage (ICH) should undergo a non-contrast CT or MRI immediately to confirm the diagnosis. Both forms of imaging have been shown to accurately detect acute intracranial hemorrhage (Chalela et al. 2007, Fiebach et al. 2004). Given that an underlying macrovascular cause is responsible for 15%-25% of non-traumatic ICHs, further imaging studies should be conducted using CT angiography, MR angiography or digital subtraction angiography to detect possible arteriovenous malformations, aneurysms or cases of cerebral venous sinus thrombosis. In the DIAGRAM study, Van Ash et al. (2015) estimated the diagnostic yield and accuracy of CTA performed in the acute phase after non-contrast CT, and with the addition of MRI/MRA and then digital subtraction angiography combined (DSA), if the results of the CTA scans were negative. In a cohort of 298 patients, an underlying vascular cause was identified in 69 patients (23%), using the reference standard of best available evidence from all diagnostic procedures. The diagnostic yield of CTA was 17%, 18% with the addition of MRI/MRA and 23% with the addition of DSA. The positive predictive value (PPV) of CTA was 72% (95% CI 60% to 82%). The addition of MRI/MRA increased PPV to 77%, (95% CI 65% to 86%), while addition of DSA increased it to 100% (95% CI 80%-100%). A single cavernoma was not identified using any of the imaging techniques. The accuracy of CTA to identify vascular lesions compared with DSA reported in other studies has been higher. In another DIAGRAM publication, younger age, lobar or posterior fossa location of ICH, absence of neuroimaging markers of cerebral small vessel disease, and a positive or inconclusive CTA were independent predictors for an ultimate macrovascular cause for the ICH being identified within 1 year of follow-up (Hilkens et al. 2017). Josephson et al. (2014) examined the diagnostic test accuracy of CTA and MRA versus intra-arterial digital subtraction angiography (IADSA) for the detection of intracranial vascular malformations. Eight studies compared CTA with IADSA and 3 studies compared MRA with IADSA. The sensitivity and specificity of both strategies was excellent (CTA: sensitivity 0.95, specificity 0.99; MRA: 0.98 and 0.99). Wong et al. (2011) reported the sensitivity, specificity and accuracy of CTA to be 100%, 98.6% and 99.1%, respectively, in a prospective sample of 109 patients, while Delgado Almandoz et al. (2009) reported the respective sensitivity and specificity as 96.1% and 98.5%.

Blood Pressure Management

While the optimum blood pressure targets for patients who have experienced a spontaneous ICH are not known, systolic blood pressure (SBP) greater than 180 mm Hg is thought to increase the risks of rebleeding and hematoma expansion. While this finding suggests that steps to lower blood pressure aggressively would be beneficial, the results from several large controlled trials on the topic are not conclusive. Qureshi et al. (2016) reported in the ATACH-2 trial that intensive blood pressure management, with an SBP target of 110-139 mm Hg did not reduce the risk of death or disability at 90 days (adjusted OR=1.04, 95% CI 0.85-1.27, p=0.72), or hematoma expansion within 24 hours (adj OR=0.78, 95% CI 0.58-1.03, p=0.08), compared with standard treatment (target of 140-179 mm Hg) in 1,000 patients admitted acutely with an ICH, while recent results from a subgroup analysis of the trial (Leasure et al. 2019) suggested that patients with deep intracranial hemorrhage may benefit from intensive treatment. Within this subgroup, the risk of hematoma expansion (defined as an increase of ≥33%) was significantly lower for patients in the intensive group (adj OR=0.61, 95% CI 0.42-0.88, p=0.009. The effect of treatment was modified by deep ICH location (p for interaction=0.02), whereby patients with a basal ganglia hemorrhage benefited from intensive BP reduction and those with thalamic hemorrhages did not. In the INTERACT-2 trial, (Anderson et al. 2013), patients in the intensive treatment arm also had SBP target of <140 mm Hg. At 90 days, 52.0% of patients in the intensive group had experienced a poor outcome (mRS score 3-5) compared with 55.6% of patients in the standard treatment group (OR=0.87, 95% CI 0.75-1.01, p=0.06). There was no significant difference between groups in 90-day mortality (11.9% vs. 12.0%, OR=0.99, 95% CI 0.79-1.25, p=0.96). There was, however, a significant shift towards the distribution of mRS scores favouring less disability among patients in the intensive group (OR=0.87, 95% CI 0.77-1.00, p=0.04). In contrast, data from the INTERACT 1 study showed that early intensive blood pressure lowering reduced hematoma growth (Anderson et al. 2008). Recent evidence from the EnRICH trial (Meeks et al. 2019) indicates blood pressure variability in the hyperacute and acute periods may play a more important role in outcome, whereby high variability was associated with poorer outcomes.

Hemostatic Therapies

Although not currently recommended for use in spontaneous ICH, another potential treatment that may help to optimize hemostasis and minimize hematoma expansion is recombinant activated factor VII (rFVIIa). In a recent trial that included 69 patients with primary spontaneous acute ICH who were spot-sign positive and randomized to receive rFVIIa (80 µg/kg or placebo), there were no significant differences between groups in the change (increase) in median parenchymal ICH volume from baseline to 24 hours (2.5 vs. 2.6 mL, p=0.89), or in median total hemorrhagic volume (3.2 mL vs. 4.8 mL, p=0.91) (Gladstone et al. 2019). Results of the FAST II (Mayer et al. 2005) and FAST III (Mayer et al. 2008) trials, suggested that treatment with rFVIIa could help to blunt the increase in ICH volume at 24 hours post treatment; however, the trials conflicted with respect to functional outcome. The FAST III trial did not report a significant difference in the proportion of patients with death or severe disability at 90 days, while FAST II reported a lower proportion in active treatment group patients. The authors of a recent Cochrane review (Al-Shahi Salman et al. 2018) stated that they could not draw firm conclusions of the benefit of blood clotting factors in the treatment of ICH, but noted ongoing research in subgroups (e.g. younger patients, earlier time windows). Other hemostatic therapies are under investigation. The benefits of the antifibrinolytic agent tranexamic acid in major trauma have increased interest in its potential benefits in spontaneous ICH. In the TICH-2 trial, the use of tranexamic acid (1 g bolus, followed by 1 g infused over 8 hours) was shown to be safe, seemed to reduce hematoma expansion and reduced early deaths, but ultimately did not improve functional outcomes at 90 days in spontaneous ICH patients treated within 8 hours of symptom onset (Sprigg et al. 2018).

Management of Anticoagulation

For patients who had been managed with warfarin prior to ICH, the results of the INCH trial (Steiner et al. 2016) indicate that treatment with prothrombin complex concentrate (PCC) is superior to intravenous fresh frozen plasma (FFP). The trial was halted early due to safety concerns, after significantly more patients in the PCC group achieved anticoagulation reversal (INR ≤1.2) within 3 hours after treatment (67% vs. 9%, OR=30.6, 95% CI 4.7-197.9, p=0.0003). There are other options when treating patients taking non-vitamin K oral anticoagulants. Treatment with idarucizumab, has been shown to be effective in reversing anticoagulation for patients requiring surgery or other invasive

procedures, who had been previously receiving treatment with the direct oral anticoagulation agent, dabigatran (Pollack et al. 2015). The ANNEXA-4 trial (Connolly et al. 2019) included patients who had sustained acute major bleeding occurring while taking a factor Xa inhibitor. The primary site of bleeding was intracranial in 64% of 352 patients enrolled. Following treatment with andexanet, there was a median reduction of 92% in anti–factor Xa activity among the patients who had been taking apixaban or rivaroxaban, while 82% of all patients who could be evaluated had excellent or good hemostasis 12 hours after infusion. The ongoing ANNEXA-I trial is assessing the clinical efficacy of random assignment to andexanet alfa compared with standard treatment (including PCC) in factor Xa inhibitor-related ICH.

Surgical Management

The role of surgical intervention for the evacuation of supratentorial ICH remains uncertain. While these procedures can stop bleeding, prevent rebleeding, and prevent secondary brain damage by removing the mass effect, trial results have been disappointing. In the Surgical Trial in Intracerebral Hemorrhage (STICH) trial, 1,033 patients with CT evidence of a spontaneous ICH that had occurred within 72 hours were randomized to early (within 24 hours) surgery for evacuation of the hematoma or to initial conservative treatment (Mendelow et al. 2005). There was no difference in the percentage of patients with a favourable outcome, which was defined based on initial prognosis. 26% of patient in the early surgical group vs. 24% of patients in the medical management group had a favourable outcome (OR=0.89, 95% CI 0.66-1.19, p=0.414, absolute benefit=2.3, 95% CI -3.2 to 7.7). There was speculation that the null findings may have been attributed, in part, to the inclusion of patients with intraventricular hemorrhages with poorer prognosis and the late timing of intervention. Therefore, in the Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II) trial (Mendelow et al. 2013), 601 patients were randomized to early craniotomy (within 12 hours) to evacuate hematoma or treated conservatively, following spontaneous superficial ICH affecting the lobar region, within 1 cm of the cortex and without ventricular extension, the subgroup of patients thought to be most likely to benefit. While there were no differences between groups in the proportion of patients who experienced a good outcome at 6 months (41% surgical group vs. 38% medical management group; OR=0.86, 95% CI 0.62-1.20, p=0.367) or who had died (18%. surgical vs. 24% medical management, OR=0.71, 95% CI 0.48-1.06, p=0.095), patients with poor prognosis were more likely to have a favourable outcome (OR=0.49, 95% CI 0.26-0.92, p=0.04). In contrast, patients with a good prognosis were no more likely to benefit from early surgery (OR=1.12, 95% 0.75-1.68, p=0.57). The results of a patient-level meta-analysis, which included the results from 8 RCTs indicated that the odds of unfavourable outcome at 3-6 months were significantly reduced among persons aged 50-69 years, in those who received surgery within 8 hours of the event, in those with baseline hematoma volumes of 20-50 mLs and with baseline Glasgow Coma Scale (GCS) score was between 9 and 12 (Gregson et al. 2012).

Minimally invasive surgery with the addition of thrombolysis has been used to treat patients with ICH and intraventricular hemorrhages, with mixed results. In the CLEAR III trial (Hanley et al. 2017), 500 patients, with spontaneous ICH ≤30 cc and an intraventricular hemorrhage (IVH) obstructing third and/or fourth ventricles, were included. Patients were randomized to irrigation of the ventricles with a maximum dose of 12.0 mg alteplase or saline placebo via a routine extraventricular drain. Treatment with alteplase did not improve the likelihood of a good functional outcome. The proportion of patients achieving an mRS score of ≤3 at 6 months was non-significantly higher in the alteplase group (48% vs. 45%, RR=1.06, 95% CI 0.88-1.28, p=0.554), although the odds of death at 6 months were significantly reduced in the alteplase group (OR=0.50, 95% CI 0.31-0.80, p=0.004). Treatment with alteplase via the MISTIE technique significantly reduced hematoma size compared with standard care in 506 patients with supratentorial ICH of ≥30 mL, although there was no significant difference between groups in the proportion of patients who achieved a good functional outcome (mRS 0-3) at one year (45% vs. 41%)(MISTIE III,Hanley et al. 2019). One-year and 180-day mortality were both significantly lower in the MISTIE group, but not 30-day mortality.

Sex and Gender considerations:

Data on sex specific differences in ICH is limited. Future research directions *should include sex or gender specific* analysis, regardless of ICH cause and should consider biological age (specifically

across the women's lifespan), clinical presentations, hematoma location/volume, expansion/risk for expansion, imaging, therapy, functional outcomes and patient-reported outcome measures.

Prior studies have demonstrated sex-disparities in ischemic stroke, but there is still a knowledge-gap regarding the role of sex or gender on the ICH risk, clinical presentation, management and /or outcomes.

Large studies, such as the ERICH study and the MGH hospital-based ICH cohort study have observed sex-related differences in primary ICH location. Lobar ICH is more common in females, while deep ICH was more frequent in males.

In the acute setting, women do not receive less aggressive care, including surgery or palliative care, than men after controlling for the substantial comorbidity differences. However, some studies found that women are more likely to receive early DNR orders after ICH than men.

Acute Management of Intracerebral Hemorrhage
Evidence Tables and Reference List

Section Two: Inpatient Care Following Intracerebral Hemorrhage

These recommendations are specific to patients with intracerebral hemorrhage and should be considered in addition to inpatient acute stroke management as defined in the most current CSBPR Acute Stroke Management module.

Recommendations

2.0 Inpatient Care following an Intracerebral Hemorrhage

i. Medically stable patients with an acute intracerebral hemorrhage should be admitted to an acute stroke unit or neuro-intensive care unit [Evidence Level B], and undergo interprofessional stroke team assessment to determine their rehabilitation and other care needs [Evidence Level B]. *Refer to CSBPR Acute Stroke Management Section 8 for more information on stroke unit care. Refer to the CSBPR Rehabilitation and Recovery following Stroke module for additional information regarding rehabilitation assessment.*

ii. The goals of care and recovery should be established with patient and/or designated substitute decision-maker [Evidence Level B].

   a. Prognostication for the purpose of modifications to goals of care should generally be deferred for 48 to 72 hours after time of presentation, to determine the extent of deficits, response to medical therapy, and potential for worsening of condition [Evidence Level B]. *Refer to the CSBPR Acute Stroke Management Section 10 on Palliative Care for additional information.*

   b. Exceptions to deferring prognostication and conservative goals of care may include patients with pre-existing wishes to avoid invasive life-sustaining therapies because of co-morbidities (e.g. dementia) or based on their own previously expressed values [Evidence Level C].

2.1 Venous Thromboembolism (VTE) Prophylaxis

i. In the acute phase of ICH, patients should be started on intermittent pneumatic compression devices, beginning the day of admission [Evidence Level A].

ii. Graduated compression stockings are not recommended for DVT prevention [Evidence Level A].

iii. Chemoprophylaxis (low molecular weight heparin) can be initiated after 48 hours and documentation of hematoma stabilization on neuroimaging [Evidence Level B**].**

   a. Documenting hematoma stabilization requires an additional scan that is separated by at least 24 hours from the baseline scan.

2.2 Seizure Management

i. People with ICH are at a greater risk of seizures at presentation [Evidence Level B] and should be monitored clinically.

ii. Consider continuous EEG for the diagnosis of nonconvulsive status epilepticus in patients with depressed level of consciousness that is out of proportion to the size and location of ICH. [Evidence Level B].

iii. New-onset seizures in patients admitted to hospital with ICH should be treated with antiepileptic medications if they are not self-limiting [Evidence Level C].

iv. A single, self-limiting seizure occurring at the onset, or within 24 hours after an ICH (considered an “immediate” post-stroke seizure) should not be treated with long-term

anticonvulsant medications [Evidence Level C]. Short-term anticonvulsant therapy can be considered in such cases on an individual basis [Evidence Level C].

v. Patients who have an immediate post-ICH seizure should be monitored for recurrent seizure activity during routine monitoring of vital signs and neurological status. Recurrent seizures in patients with ICH should be treated as per treatment recommendations for seizures in other neurological conditions [Evidence Level C].

vi. Prophylactic use of anticonvulsants in patients with ICH is not recommended [Evidence Level B].

2.3 Increased Intracranial Pressure (ICP)

i. In cases of suspected elevated ICP, conservative methods to decrease ICP (such as elevation of head of bed 30 degrees, methods of neuroprotection (e.g., euthermia, euglycemia), analgesia, and mild sedation) are reasonable [Evidence Level C].

ii. In the absence of concerns regarding ICP, head of bed positioning does not seem to influence neurological outcomes or serious adverse events in stroke patients, including ICH [Evidence Level B].

iii. There is insufficient evidence to recommend the routine or prophylactic use of hyperosmotic agents in ICH [Evidence Level C].

   a. Hyperosmotic agents (mannitol and/or 3% normal saline) can be considered as a temporizing measure to decrease ICP in ICH patients with clinical signs of herniation prior to surgical intervention [Evidence Level C].

iv. Use of corticosteroids to treat ICP in ICH may cause harm, has no proven benefits, and therefore is not recommended [Evidence Level B].

Clinical Considerations for Section 2.3:

i. Hyperthermia and hyperglycemia have been associated with poor outcomes in ICH patients. In the absence of randomized controlled trial research evidence, it is advisable to target normothermia and normoglycemia in hospitalized ICH patients.

ii. In patients with elevated ICP ensure to avoid compression of neck vessels, particularly when securing endotracheal tubes

2.4 Rehabilitation following intracerebral hemorrhage

Note: Rehabilitation assessment and management for people who have experienced an ICH generally follow the same approaches as for people with other causes of stroke. Therefore, the CSBPR Recommendations for Rehabilitation and Recovery Following Stroke module apply to this patient population. This includes early assessment during acute inpatient care

i. Patients with ICH should have continued monitoring for rehabilitation readiness beyond conventional time frames used in ischemic stroke patients due to emerging evidence regarding their prolonged recovery trajectories [Evidence Level B]. *Note: Early assessments for rehabilitation readiness may underestimate rehabilitation potential.*

Rationale

Stroke unit care reduces the likelihood of death and disability by as much as 30 percent for men and women of any age with mild, moderate, or severe stroke. Stroke unit care is characterized by a coordinated interdisciplinary team approach for preventing stroke complications, preventing stroke recurrence, accelerating mobilization, and providing early rehabilitation therapy. Evidence suggests that stroke patients treated on acute stroke units have fewer complications, earlier mobilization, and

pneumonia is recognized earlier. Patients should be treated in a geographically defined unit, as care through stroke pathways and by roving stroke teams do not provide the same benefit as stroke units. Access to early rehabilitation is a key aspect of stroke unit care. For patients with stroke, rehabilitation should start as early as possible and rehabilitation should be considered an intervention that can occur in any and all settings across the continuum of stroke care.

System Implications

1. Organized systems of stroke care including stroke units with a critical mass of trained staff (interdisciplinary team). If not feasible, then mechanisms for coordinating the care of stroke patients to ensure use of best practices and optimal outcomes.
2. Protocols and mechanisms to enable the rapid transfer of ICH stroke patients from the Emergency Department to a specialized stroke unit as soon as possible after arrival in hospital, ideally within the first six hours.
3. Comprehensive and advanced stroke care centres should have leadership roles within their geographic regions to ensure specialized stroke care access is available to patients who may first appear at general health care facilities (usually remote or rural centres) and facilities with basic stroke services only.
4. Telestroke service infrastructure and utilization should be optimized to ensure access to specialized stroke care across the continuum to meet individual needs (including access to rehabilitation and stroke specialists) including the needs of northern, rural and remote residents in Canada.
5. Information on geographic location of stroke units and other specialized stroke care models available to community service providers, to facilitate navigation to appropriate resources and to strengthen relationships between each sector along the stroke continuum of care.

Performance Measures

System Level Performance Measures:

1. Proportion of ICH patients treated in a Level 4 or Level 5 stroke centre

Clinical Performance Measures:

1. Number of ICH patients who are admitted to hospital and treated on a specialized stroke unit at any time during their inpatient hospital stay for an acute stroke event (numerator) as a proportion of total number of stroke patients admitted to hospital (core).
2. Proportion of ICH patients who die in hospital within 7 days and within 30 days of hospital admission for an index stroke (core).
3. Proportion of total time in hospital for an acute ICH spent on a stroke unit.
4. Proportion of patients admitted to a stroke unit, who arrive in the stroke unit within 24 hours of Emergency Department arrival.
5. Percentage of patients admitted to hospital with a diagnosis of acute stroke who experience one or more complications during hospitalization (deep venous thrombosis, pulmonary embolus, secondary cerebral hemorrhage, gastrointestinal bleeding, pressure ulcers, urinary tract infection, pneumonia, seizures [or convulsions]) during inpatient stay.
6. Median length of stay during acute phase of care for ICH patients admitted to hospital (core). (Stratify by stroke type).
7. Percentage of ICH patients who experienced prolonged length of stay beyond expected length of stay as a result of experiencing one or more complications
8. Percentage of ICH patients who had a referral to specialist palliative care services during inpatient care.
9. Percentage of dying ICH patients who were placed on an end-of-life care protocol.
10. Percentage of ICH patients who die in the location specified in their palliative care plan.

Patient Oriented Outcome Measures:

1. Self-reported quality of life following ICH using a validated measurement tool.
2. Proportion of ICH patients discharged to their home or place of residence following an inpatient admission for stroke (core).
3. Family and caregiver ratings on the palliative care experience following the death in hospital of a patient with ICH.

Measurement notes:

i. Level 4 and 5 centres based on SBP criteria, these facilities include a stroke unit and access to neurosurgical services onsite

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- CoHESIVE: http://www2.phri.ca/cohesive/
- Stroke Engine: http://strokengine.ca/
- CSBPR Virtual Healthcare Toolkit: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/csbpr7-virtualcaretools-13may2020
- American College of Chest Physicians (ACCP) Anticoagulation Guidelines: http://www.chestnet.org/Guidelines-and-Resources
- Hypertension Canada Treatment Guidelines: https://guidelines.hypertension.ca/
- Canadian Stroke Best Practices Acute Stroke Management Table 2B: Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack:
- Canadian Stroke Best Practices Acute Stroke Management Appendix Three: Screening and Assessment Tools for Acute Stroke Severity

Information for People with Stroke, their Families and Caregivers

- Stroke Engine: http://strokengine.ca/
- Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Your Stroke Journey: A Guide for People Living with Stroke https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Stroke in young adults: A resource for patients and families: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final
- Stroke Resources Directory: https://www.heartandstroke.ca/services-and-resources
- Taking charge of your stroke recovery: Rehabilitation and recovery infographic https://www.heartandstroke.ca/-/media/1-stroke-best-practices/rehabilitation-nov2019/csbp-infographic-rehabilitation
- Taking charge of your stroke recovery: Transitions and community participation infographic https://www.heartandstroke.ca/-/media/1-stroke-best-practices/transition-of-care-nov2019/csbp-infographic-transitions-and-participation
- Taking charge of your stroke recovery: 2020 Virtual healthcare checklist infographic https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbp-infographic-virtual-healthcare-checklist

- Hypertension Canada Patient Resources: https://hypertension.ca/hypertension-and-you/
- Heart and Stroke Foundation Canadian Partnership for Stroke Recovery: https://www.canadianstroke.ca/

Summary of the Evidence 2020

Specialized Units

While it is now well-accepted that patients with ischemic stroke admitted to a stroke unit featuring dedicated beds and staff have better outcomes compared with patients admitted to general or less-specialized units, there is also evidence that the subset of patients who have experienced ICH realize the same benefits. In a systematic review, Langhorne et al (2013) included the results from 8 trials in which patients with ischemic and hemorrhagic stroke were randomized to receive care on a stroke unit or an alternative setting. Stroke unit care was associated with significant reductions in the risk of death or dependency (mRS 3-5) (RR=0.81, 95% CI 0.71-0.92, p<0.0001) and death (RR=0.79, 95% CI 0.64-0.97, p=0.02), with no significant interactions based on stroke type. Diringer & Edwards (2001) reviewed the charts of 1,038 patients who had been admitted to either a neuro-ICU (n=2) or a medical and/or surgical ICU (n=40) following ICH and reported that after adjusting for demographics, severity of ICH, and ICU and institutional characteristics, admission to a general ICU was associated with an increase in hospital mortality (OR=3.4; 95% CI 1.65–7.6). Additional independent predictors of higher mortality were advancing age, lower GCS scores, fewer ICH patients treated and smaller ICU size. In contrast, having a full-time intensivist was associated with lower mortality rate. Ronning et al. (2001) also reported improved survival during the first 30 days and one year following admittance to an acute stroke unit care. At 30 days, fewer patients in the stroke unit group were dead (39% vs. 63%, adjusted OR=0.40, 95% CI 0.17-0.94). There was no difference in one-year mortality between groups (52% vs. 69%, adjusted OR=0.58, 95% CI 0.24-1.38), or the number of patients discharged home between groups (27% vs. 52%, adjusted OR=1.60, 95% 0.62-4.00).

Venous Thromboembolism (VTE) Prophylaxis

The use of external compression stockings/devices was investigated in a series of three large, related RCTs, the Clots in Legs Or sTockings after Stroke (CLOTS) trials. In the third trial, CLOTS 3 (Dennis et al. 2013), patients were randomized to a wear thigh length intermittent pneumatic compression (IPC) device or to no IPC for a minimum of 30 days. Of the 2,876 patients included, 13% had suffered an ICH. The mean duration of IPC use was 12.5 days and 100% adherence to treatment was achieved in only 31% in the IPC group. The incidence of proximal DVT within 30 days was significantly lower for patients in the IPC group (8.5% vs. 12.1%, OR=0.65, 95% CI 0.51-0.84, p=0.001, ARR=3.6%, 95% CI 1.4%-5.8%). There were no significant differences between groups for the outcomes of: death at 30 days (10.8% vs. 13.1%, p=0.057), symptomatic proximal DVT (2.7% vs. 3.4%, p=0.269), or pulmonary embolism (2.0% vs. 2.4%, p=0.453). The incidence of any DVT (symptomatic, asymptomatic, proximal or calf) was significantly lower for IPC group (16.2% vs. 21.1%, OR=0.72, 95% CI 0.60-0.87, p=0.001). At 6 months, the incidence of any DVT remained significantly lower in the IPC group (16.7% vs. 21.7%, OR=0.72, 95% CI 0.60-0.87, p=0.001). The incidence of any DVT, death or PE also remained significantly lower for IPC group (36.6% vs. 43.5%, OR=0.74, 95% CI 0.63-0.86, p<0.0001). In a systematic review and meta-analysis, Paciaroni et al. (2011) reported that early treatment with UFH and LMWH initiated between 1-6 days following ICH led to a significant reduction in the incidence of pulmonary embolus (1.7% vs. 2.9%; P = 0.01), without an increase in hematoma expansion. In a small randomized trial of 68 patients with ICH, participants randomized to LWMH on day 2 following their ICH experienced fewer pulmonary emboli than those randomized to initiate treatment on days 4 and 10, without an apparent increase in rebleeding (Boeer et al. 1991).

Seizure Management

Following ICH, patients are at increased risk of seizures. Early-onset seizure typically occur at or near event onset, and are thought to be less common, while late-onset seizures occur 6-12 months post event. Whether to treat a first occurrence of a post stroke seizure following an ICH, is a topic of debate.

Individual patient risk factors should be considered. However, long-term use of antiepileptic drugs (AED) has not been shown to be effective at reducing the odds of recurrent seizure (Angriman et al. 2019), and may be associated with poor outcome (Messe et al. 2009). There are very few studies that have the use of AEDs in stroke, generally and following ICH, specifically.

Increased Intracranial Pressure

While a wide variety of nonsurgical interventions are used commonly to lower intracranial pressure following ICH, including head elevation, hyperosmotic agents, hyperventilation, analgesia, and sedation, RCT evidence of their effectiveness is lacking. Head- PoST (Anderson et al. 2017) randomized over 11,000 patients following stroke to receive care in either a lying-flat position or a sitting-up position with the head elevated to at least 30 degrees, which was initiated as soon as possible and maintained for 24 hours). There were no significant differences between groups in any of the primary or secondary clinical outcomes (mRS scores, death or major disability at 7 and 90 days). The results were similar in the subgroup of 8% of patients with ICH.

Acute Management of Intracerebral Hemorrhage

Evidence Tables and Reference List

Section Three: Secondary Stroke Prevention in an Individual with Intracerebral Hemorrhage

This section addresses secondary prevention management issues specific to individuals who have experienced an intracerebral hemorrhage (intraparenchymal and intraventricular hemorrhages) General principles of vascular health and risk reduction that are addressed in the CSBPR Secondary Prevention of Stroke Module may also apply to this population where they are non-specific to stroke type. The topics included here may overlap with the broader prevention module where they may have different levels of evidence available

Recommendations

3.1 Risk Assessment

i. Persons at risk of stroke and patients who have had an ICH should be assessed for vascular disease risk factors (such as diet, sodium intake, waist-to-hip ratio, sedentary lifestyle, alcohol intake, blood pressure, and smoking) [Evidence Level B]. *Please refer to the CSBPR Secondary Prevention of Stroke Module for additional information.*

ii. Patients who experience an ICH should be assessed for underlying etiology and risk of recurrence [Evidence Level B].

   a. The assessment of recurrent risk for an ICH should be based on clinical factors (including age, hypertension, ongoing anticoagulation, prior lacunar stroke) and neuroimaging (lobar location of index ICH suggestive of cerebral amyloid angiopathy, presence of associated convexal subarachnoid hemorrhage, and presence and number of cerebral microbleeds and/or cortical superficial siderosis on susceptibility weighted or gradient echo MRI sequences) [Evidence Level B].

Note: validated risk assessment tools for intracerebral hemorrhage recurrence have not been published.

Clinical Considerations for Section 3.1

i. In the absence of tissue diagnosis, probable cerebral amyloid angiopathy can be diagnosed in hospital populations based on the modified Boston criteria as follows: Age ≥55 years; (and) clinical data and MRI demonstrating multiple macro or microhemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed), or a single lobar, cortical or corticosubcortical macro- or microhemorrhage and cortical superficial siderosis; (and) absence of other cause of hemorrhage or cortical superficial siderosis.

3.2 Lifestyle Management:

i. For individuals with intracerebral hemorrhage, healthcare professionals should recommend increased physical activity, healthy diet, reductions of alcohol consumption, cessation of smoking, and cessation of cocaine/amphetamine use where relevant (Evidence Level C) . *Refer to Section 2 CSBPR Secondary Prevention of Stroke Module for recommendations on lifestyle management after stroke.*

Clinical Consideration for Section 3.2

i. There is no evidence to restrict air travel in patients post ICH above and beyond routine limitations following stroke.

3.3 Blood Pressure Management Following Intracerebral Hemorrhage

i. Long-term, blood pressure should be aggressively monitored, treated and controlled [Evidence level A] to sustain a target blood pressure consistently lower than 130/80 mmHg [Evidence Level B].

ii. *For specific agents to manage blood pressure, refer to Hypertension Canada's current blood pressure management guidelines.*

Clinical Considerations for Section 3.3

i. Home blood pressure monitoring devices should be encouraged to achieve blood pressure targets.

3.4 Antithrombotic Therapy following Intracerebral Hemorrhage

i. In ICH patients with an indication for anticoagulant treatment, the decision to initiate or resume anticoagulation should be individualized according to the patient's risk of recurrent hemorrhage and thromboembolism [Evidence Level C].

ii. If anticoagulation is deemed necessary and where direct oral anticoagulant (DOAC) treatment is indicated (i.e. atrial fibrillation), DOAC therapy is favored over warfarin. This is based, however, primarily on their reduced rates of ICH in atrial fibrillation randomized trials where ICH patients were excluded [Evidence Level B].

   a. DOACs should not be used in patients with mechanical heart valves and intracerebral hemorrhage [Evidence Level B].

iii. Where indicated, antiplatelet monotherapy can be considered in patients deemed too high risk for anticoagulation [Evidence Level B].

iv. In patients with an indication for continued antiplatelet treatment, resuming antiplatelet therapy is reasonable [Evidence Level B].

v. The optimal timing and strategy regarding antithrombotic therapy (antiplatelet or anticoagulant) following an intracerebral hemorrhage is uncertain and should be individualized to the patient [Evidence Level C].

Clinical Consideration for Section 3.4

i. Consultation with experts in cerebrovascular disease may assist in clinical decision-making regarding antithrombotic therapy following ICH.

ii. Randomized trials are ongoing regarding the net benefit and safety of direct oral anticoagulant (DOAC) therapy and left atrial appendage closure in patients with ICH and atrial fibrillation. These patients should be assessed by an expert in cerebrovascular diseases if possible, to support decision-making on management.

3.5 Statin Therapy in Intracerebral Hemorrhage:

i. There is no role for statin therapy in the secondary prevention of ICH. Statin therapy should not be initiated for secondary prevention of intracerebral hemorrhage [Evidence Level C].

ii. For intracerebral hemorrhage patients who have a clear concomitant indication for cholesterol lowering treatment, statin therapy should be individualized and should take into account the patient's overall thrombotic risk as well as the possibility of increased ICH risk with statin therapy [Evidence Level C]. *Refer to CSBPR Prevention of Stroke module section 4 on Lipid Management for additional information.*

Clinical Considerations for Section 3.5

i. An ongoing clinical trial (SATURN) addressing this question may potentially inform clinical decision-making for these patients. Until these results are available, decisions regarding statin therapy should be made based on risk/benefit ratio in consultation with an expert in cerebrovascular disease.

3.6 Functional Assessment

i. Following an ICH, patients should be assessed for neurological impairments and functional limitations when appropriate (e.g., cognitive evaluation, screening for depression, screening of fitness to drive, need for potential rehabilitation therapy, and assistance with activities of daily living), especially for patients who are not admitted to hospital [Evidence Level C]. *Refer to CSBPR Rehabilitation Module Recommendations 5.1 and 5.6 for additional information.*

ii. Patients found to have any continued or new neurological impairments and functional limitations should be referred to the appropriate rehabilitation specialist for in-depth assessment and ongoing management [Evidence Level C].

Rationale

The incidence of ICH is approximately 20/100,000 in the western populations (van Asch et al. 2010), with a cumulative risk of recurrence of 1% to 7% per year (Poon et al. 2014). The rate of recurrence is less in ICH confined to deep structures (1-2% per annum; deep grey/white matter, brainstem) relative to lobar ICH (5-8% per annum; cortical, corticosubcortical regions). ICHs carry the highest mortality rate amongst all stroke subtypes, averaging 55% at 1 year, while only 25% of ICH victims resume functional independence. ICH is a major contributor to stroke-related cognitive impairment with 35% of survivors demonstrating progressive cognitive decline (Benedictus et al. 2015). Given their severity, ICH patients add a significant burden to the Canadian Health Care System with a median cost of $10,500, to upwards of $260,000, per hospitalization alone. (Specogna et al. 2014).

ICH incidence is associated with modifiable lifestyle factors such as alcohol consumption, smoking, unhealthy diet, elevated waist-to-hip ratio and sedentary lifestyle. ICH recurrence can be considerably reduced by long-term blood pressure reductions (Benavente et al. 2013, Arima et al. 394). The goal is of spontaneous ICH prevention management is to identify and mitigate modifiable risk factors in ICH survivors, to prevent further hemorrhagic events and loss of functional independence. Many uncertainties persist regarding optimal antithrombotic therapy and lipid lowering therapy in ICH patients who have comorbid vaso-occlusive diseases.

System Implications

1. Education for the public and healthcare providers about the importance of risk factor modification and in particular blood pressure control in the management of ICH patients in order to reduce the risk of recurrent events. Patients and families will also require ongoing education and support related to prevention and management of ICH.
2. ICH-specific processes and protocols to enable rapid access to expertise for patients with ICH in community healthcare settings and acute healthcare facilities.
3. Processes that ensure referral of ICH patients to stroke prevention clinics from surgical and other medical subspecialties.
4. Establishing multidisciplinary pathways for risk-benefit assessment of management decisions in ICH patients who have comorbid vaso-occlusive disease.

Performance Measures

System Level Performance Measures:

1. The proportion of ICH patients living independently in the community at 90 days and one year following index ICH.

Clinical Performance Measures:

1. Proportion of people who experienced an initial ICH stroke who then have a recurrent stroke.
2. Median time between first ICH and recurrent stroke.
3. Readmission rates to hospital with complications following index ICH (such as venous and systemic thromboembolic events, infections, hydrocephalus, aspiration pneumonia, post-ICH seizures, infection, and low-trauma fracture)

Patient Oriented Outcome Measures:

1. Self-reported quality of life following ICH using a validated measurement tool.
2. Functional ability (mRS score) at 90 days and one year following ICH

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- CoHESIVE: http://www2.phri.ca/cohesive/
- Stroke Engine: http://strokengine.ca/
- CSBPR Virtual Healthcare Toolkit: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/csbpr7-virtualcaretools-13may2020
- American College of Chest Physicians (ACCP) Anticoagulation Guidelines: http://www.chestnet.org/Guidelines-and-Resources
- Hypertension Canada Treatment Guidelines: https://guidelines.hypertension.ca/

Information for People with Stroke, their Families and Caregivers

- Stroke Engine: http://strokengine.ca/
- Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Your Stroke Journey: A Guide for People Living with Stroke https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Stroke in young adults: A resource for patients and families: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final
- Stroke Resources Directory: https://www.heartandstroke.ca/services-and-resources
- Taking charge of your stroke recovery: Rehabilitation and recovery infographic https://www.heartandstroke.ca/-/media/1-stroke-best-practices/rehabilitation-nov2019/csbp-infographic-rehabilitation
- Taking charge of your stroke recovery: Transitions and community participation infographic https://www.heartandstroke.ca/-/media/1-stroke-best-practices/transition-of-care-nov2019/csbp-infographic-transitions-and-participation
- Taking charge of your stroke recovery: 2020 Virtual healthcare checklist infographic
- https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbp-infographic-virtual-healthcare-checklist
- Hypertension Canada Patient Resources: https://hypertension.ca/hypertension-and-you/

- Heart and Stroke Foundation Canadian Partnership for Stroke Recovery: https://www.canadianstroke.ca/
- Heart and Stroke information on: Stroke Medications

Summary of the Evidence 2020

Lifestyle

Certain lifestyle risk factors may increase the risk of ICH to a greater extent compared with ischemic stroke. Smoking, a sedentary lifestyle and excessive alcohol consumption are of particular concern. In the second phase of the INTERSTROKE study (O'Donnell et al. 2016), the risk of ICH was increased to a greater degree compared with ischemic stroke among persons who consumed higher amounts of alcohol, defined as >14 drinks/week in women or >21 drinks/ week in men, and in those who did not engage in at least four hours of moderate or strenuous leisure activity, weekly. In phase one of the INTERSTROKE study, (O'Donnell et al. 2010) consuming >30 drinks/month or binge drinking was associated with an increased risk of hemorrhagic stroke compared with never/former drinkers. The risk of hemorrhagic stroke was higher than ischemic stroke. Zang et al. (2014) reported that while low-to-moderate alcohol intake was not associated with hemorrhagic stroke risk, an intake of ≥45 g/day was associated with increased risk was, in a systematic review that included the results of 27 prospective studies.

Blood Pressure

In terms of treatment for secondary prevention, long-term intensive blood pressuring lowering to <130/80 mmHg, was shown to be safe and reduce the risk of future ICH (63% RRR) in the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial (Benavente et al. 2013). This finding was among patients with lacunar stroke, who share a prevalent underlying pathophysiology (arteriolosclerosis or hypertensive arteriopathy) with ICH. Moreover, a mean blood pressure reduction of 9/4 mmHg in participants within PROGRESS trial reduced the risk of cerebral amyloid angiopathy-related ICH by 77% and hypertensive arteriopathy-related ICH by 46% (Arima et al. 2010).

Statin Use

Administration of statins, used for the prevention of ischemic strokes, has been associated with an increased risk of ICH. In the Stroke Prevention by Aggressive Reduction in Cholesterol (SPARCL) trial (Amarenco et al. 2006), 4,732 patients with a previous stroke were randomly assigned to receive either 80 mg/day atorvastatin or matching placebo for an average of 4.9 years. While the risk of ischemic stroke was reduced significantly for patients in the statin group, the risk of ICH was increased significantly (55 vs. 33, HR=1.66 95% CI 1.08-2.55, p=0.020). Independent risk factors for ICH included treatment with atorvastatin (HR=1.69, 95% CI 1.10-2.60, p=0.02), male gender, previous ICH and stage 2 hypertension (Goldstein et al. 2008). Pooling the results from two secondary prevention trials (SPARCL and the Heart Protection Study-including patients with prior cardiovascular disease), Amarenco & Labreuche (2009) reported that statin therapy was associated with a significantly increased risk of ICH (RR=1.73, 95% CI 1.19-2.50). However, when analyzed separately, statin use was not associated with an increased risk of ICH in subgroup analysis of primary prevention studies (n=9, RR=0.81, 95% CI 0.60-1.08). Ziff et al. (2019) included the results of 51 studies examining the use of statin therapy in patients with previous ischemic or hemorrhagic stroke. Among patients with previous ICH (n=15 studies), statins did not significantly increase the risk of recurrent ICH (RR=1.04, 95% CI 0.86 to 1.25), while the risks of all-cause mortality and poor functional outcome were reduced significantly with statin therapy (RR=0.49, 95% CI 0.36-0.67 and RR=0.71, 95% CI 0.67-0.75). McKinney & Kostis (2012) included 31 RCTs (n=182,803 patients) in a meta-analysis examining the use of statins (high vs. low-dose statins, n=6 and any statin vs. control or usual care, n=25 trials) for stroke prevention with a mean duration of follow-up of 46 months. Using the results from all trials, any statin use was not associated with a significantly increased risk of ICH (0.39% vs. 0.35%, OR=1.08, 95% CI 0.88-1.32, p=0.47). In subgroup analysis of primary and secondary prevention trials, the risks of ICH were also not significantly increased with statin use (OR=0.86, 95% CI 0.75-1.23, p=0.77 and

OR=1.26, 95% CI 0.91-1.73, p=0.54, respectively). The ongoing SATURN trial is assessing the effect of statin continuation compared with discontinuation on recurrent ICH rates following lobar ICH.

Antithrombotics

The decision whether to resume antithrombotic therapy for patients following an ICH can be challenging due to the increased risk of recurrence. This risk must be balanced with the prevention of a future ischemic event, particularly for patients with nonvalvular atrial fibrillation. While the issue remains unresolved and is best approached on an individual basis, the evidence from recent studies suggest that the benefits may outweigh the risks. The RESTART trial (2019), randomized 537 participants with spontaneous ICH, to receive antiplatelet therapy (either aspirin, clopidogrel, and/or dipyridamole) or to avoid antithrombotic therapy. Antiplatelet therapy did not increase the risk of recurrent ICH (aHR 0.51 [95% CI 0.25-1.03, p=0.06), and was associated with a 35% (p=0.025) relative risk reduction in the secondary composite outcome of non-fatal myocardial infarction, non-fatal stroke and vascular death. Further reassurance is provided in the RESTART MRI subgroup analyses that did not demonstrate any treatment modification according to ICH location, or the presence and burden of MRI markers of cerebral small vessel disease, including cerebral microbleeds and cortical superficial siderosis (Al-Shahi Salman et al. 2019). Ottosen et al. (2016) included 6,369 patients presenting with first-ever spontaneous, non-traumatic ICH, who survived for the first 30 days. During a median of 2.3 years of follow-up, post-discharge use of oral antithrombotics (including oral anticoagulants and antiplatelets), which was initiated most frequently within 3-6 months of stroke, was associated with a significantly reduced risk of death (HR=0.59, 95% CI 0.43-0.82) and thromboembolic events (HR=0.58, 95% CI 0.35-0.97), with no increased risk of major bleeding (HR=0.65, 95% CI 0.41-1.02) or recurrent ICH (HR=0.90, 95% CI 0.44-1.82). Kuramatsu et al. (2015) compared ICH recurrence of 719 patients who restarted oral anticoagulation (OAC) therapy with vitamin K antagonists, with patients who did not restart OACs following oral anticoagulant-related ICH. The risk of ischemic complication was significantly higher for patients who did not resume OACs (15.0 vs. 5.2%, p<0.01), while the risk of hemorrhagic complications was not (8.1 vs. 6.6%, p=0.48). Nielsen et al. (2015) included 1,752 patients with nonvalvular atrial fibrillation who were subsequently admitted to hospital with an intracranial hemorrhage, who survived for the first 6 weeks and had been receiving anticoagulation therapy for at least 6 months prior to the event. The combined risk of ischemic stroke/systemic embolism and all-cause mortality was significantly reduced compared with patients who did not resume oral anticoagulation therapy (HR=0.55, 95% CI 0.39-0.78), without a significant risk of recurrent ICH or extracranial bleeding. Pooling the results from these 3 studies and 5 others, Murthy et al. (2017) reported there was no significantly increased risk of recurrent ICH after resumption of anticoagulation therapy (RR=1.01, 95% CI 0.58-1.77) while the risk of stroke or MI was significantly lower (RR=0.34, 95% CI 0.25-0.45). Similar net benefit seems to generalize to higher risk patients with lobar ICH, and may generalize to those with cerebral amyloid angiopathy. However, confounding by indication limits the interpretation of these observational studies. In the Canadian-led NASPAF-ICH trial presented at the 2020 International Stroke Conference there was only one primary outcome of recurrent ICH and/or ischemic stroke amongst 30 participants with atrial fibrillation and previous ICH randomized (2:1) to standard dosing non-vitamin K antagonist oral anticoagulant (NOAC) therapy or aspirin 81 mg daily over mean follow-up of 1.53 years (SD 0.54). This event was an ischemic stroke occurring in a patient with temporary discontinuation of assigned aspirin therapy due to a major genitourinary hemorrhage. There was no recurrent ICH in either arm of the study. All participants had close home blood pressure monitoring to ensure target <130/80 mm Hg. These preliminary results are being investigated further in ongoing randomized trials.

Secondary Stroke Prevention for Intracerebral Hemorrhage
Evidence Tables and Reference List

APPENDIX ONE

Canadian Stroke Best Practice Recommendations Management of Spontaneous Intracerebral Hemorrhage Writing Group 2020 and Manuscript authors

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Shoamanesh Ashkan	MD, FRCPC Director, Stroke Fellowship Program; Assistant Professor of Medicine (Neurology), McMaster University, Staff Physician Hamilton Health Sciences, David Braley Cardiac, Vascular and Stroke Research Institute; Marta and Owen Boris Chair in Stroke Research and Care, McMaster University; Director, Hemorrhagic Stroke Research Program, Population Health Research Institute	ON	**Advisory Boards:** ApoPharma Inc, Bristol-Myers Squibb, Servier Canada Inc, Bayer AG, Daiichi Sankyo Company Ltd. **Speakers Bureau:** Servier Canada Inc, Bayer AG **Research Funding:** Bristol-Myers Squibb, Servier Canada Inc, Bayer AG, Daiichi Sankyo Company Ltd., Portola
Gioia, Laura C.	MD FRCPC MSc Assistant Professor of Neurology, University of Montreal; Stroke Neurologist, CHUM-Centre Hospitalier de l'Université de Montréal	QC	**Clinical trial patient recruitment:** NASPAF-ICH, ENRICH-AF, ESCAPE NA1 **Speaker's honoraria:** Bayer, Servier, BMS Pfizer
Castellucci, Lana A.	MD, FRCPC, MSc Associate Scientist, Clinical Epidemiology Program Ottawa Hospital Research Institute Assistant Professor, University of Ottawa, Faculty of Medicine, Department of Medicine Divisions of Hematology and General Internal Medicine, The Ottawa Hospital	ON	**Speaker's honoraria:** Bayer, BMS-Pfizer, LEO Pharma, Sanofi, Servier
Cayley, Anne	RN(EC), MN-NP(Adult) Nurse Practitioner, Toronto West Regional Stroke Program, University Health Network, Canadian Neuroscience Nurses Association	ON	**Clinical trial study coordinator:** UHN
Crowther, Mark	MD, MSc, FRCPC, FRSC Chair, Department of Medicine, Leo Pharma Chair in Thromboembolism Research, McMaster University	ON	**Advisory Board:** BMS Canada (Sept 2017); CSL Behring (Sept 2017); Servier (Dec 2018); Asahi Kasei (Dec 2018); Precision Biologics (Nov 2019); Hemostasis Reference Lab (ongoing)

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
			Payment received: McMaster University (ongoing); University of Pennsylvania (May 2018); Thrombosis & Haemostasis Society of North America (May 2018); Blood Systems Inc (July 2018); St. Joseph's Healthcare Hamilton (July 2018); Illinois Association of Blood Banks (May 2019); American Society of Hematology (July 2019); Population Health Research Institute (Oct 2019); London Health Sciences Centre (Oct 2019); Antibody Communication (Oct 2019); The Anticoagulant Forum (Nov 2019); The Nova Scotia Health Authority (Nov 2019); The Canadian Medical Protective Association (ongoing); UpToDate (ongoing); American Society of Hematology (June 2020) - personal payments
de Wit, Kerstin	McMaster University, Assistant Professor, Division of Emergency Medicine, Department of Medicine, Emergency Medicine and Thrombosis Physician, Hamilton Health Sciences	ON	**Research grant:** Bayer
English, Shane W.	MD, FRCPC, MSc Associate Scientist, Clinical Epidemiology Program Ottawa Hospital Research Institute Assistant Professor, Department of Medicine (Critical Care) and School of Epidemiology and Public Health, UOttawa	ON	No conflicts to declare
Hoosein, Sharon	RN-EC, MN, CNN(c) Nurse Practitioner, Stroke Unit Trillium Health Partners, Assistant Clinical Professor, McMaster University	ON	No conflicts to declare
Huynh, Thien	MD, MSc, FRCPC Diagnostic and Interventional Neuroradiologist, Queen Elizabeth II Health Sciences Centre, Assistant Professor, Dalhousie University	NS	No conflicts to declare

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Kelly, Michael	MD, PhD, FRCSC Professor and Head of Neurosurgery, Saskatchewan Clinical Stroke Research Chair, University of Saskatchewan, Saskatoon, Saskatchewan	SK	**Speaker bureau:** Medtronic Inc., Penumbra Inc.
O'Kelly, Cian J.	MD, MSc, FRCSC Associate Professor of Neurological Surgery, University of Alberta	AB	**Clinical trial site sub Principal Investigator:** REACT
Teitelbaum, Jeanne	MD, FRCP Clinical Professor of Neurology, Universite de Montreal, Associate Professor of Neurology Neurosurgery, McGill University, Program Director Neurocritical Care, Montreal Neurological Institute MUHC	QC	No conflicts to declare
Yip, Samuel	PhD, MD, FRCPC Clinical Associate Professor, University of British Columbia	BC	No conflicts to declare
CoHESIVE	Canada-centric International Collaborative ICH Network	Canada-wide	Sponsorship from Bayer AG, Bristol-Myers Squibb and Servier Canada Inc.
Additional Contributors to publication manuscript			
Dowlatshahi, Dar	MD PhD FRCP(C) Senior Scientist, Neuroscience Program Ottawa Hospital Research Institute Associate Professor, Medicine, School of Epidemiology and Public Health University of Ottawa Stroke Neurologist, Medicine, Neurology Ottawa Hospital Vice Chair of Research, Department of Medicine University of Ottawa	ON	No conflicts to declare
Foley, Norine	Consultant workHORSE Consulting Group		No conflicts to declare
Gubitz, Gord	MD, FRCPC Division of Neurology QEII - Halifax Infirmary (HI) Site	NS	**Operational Lead, Stroke Best Practices:** Heart and Stroke Foundation of Canada **Clinical trial collaborator:** ESCAPE NA1 (University of Calgary)

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Mountain, Anita	MD, FRCPC Dalhousie University	NS	**Clinical trial site QI:** Brain Canada, and Heart and Stroke Foundation, Canadian Partnership for Stroke Recovery
Smith, Eric E.	MD, MPH, FRCPC Professor of Neurology University of Calgary	AB	**Consulting:** Biogen, Alnylam, Javelin Medica **Royalties:** UpToDate
M. Patrice Lindsay	RN, BScN, M.Ed, PhD Director, Systems Change and Stroke Program, Heart and Stroke Foundation of Canada	ON	No conflicts to declare

Canadian Stroke Best Practice Recommendations Management of Spontaneous Intracerebral Hemorrhage External Reviewers 2020

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Aleksandra Pikula	BSc. (Hon), MD, DABPN Assistant Professor of Medicine (Neurology), University of Toronto Division of Neurology, Stroke Program, UHN/TWH Clinical Lead, Combined CNS Vasculitis and Stroke in Young Program, TWH/MSH Co-Director, Women's Neurology Fellowship, University of Toronto Director, UHN Stroke Research Program; Associate Investigator, Framingham Study, Boston	Ontario	No conflicts to declare
Rustam Al-Shahi Salman	MA (Cantab) MB BChir PhD FHEA FESO FRCP Edin Professor of Clinical Neurology (University of Edinburgh, UK) and honorary consultant neurologist (NHS Lothian, Edinburgh, UK)	Edinburgh	No conflicts to declare
Steven Greenberg	MD, PhD Director, Hemorrhagic Stroke Research Program, Vice-Chair, Faculty Development and Promotions, John J. Conway Endowed Chair in Neurology, Massachusetts General Hospital	United States	Potential conflict: Grant recipient: US National Institutes of Health

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
	Harvard medical School,		
Lisa Groulx	RN, MN, ENC(C) Clinical Educator, Professional Practice Lead-Emergency Department Guelph General Hospital	Ontario	No conflicts to declare
Carlos S Kase	MD Professor of Neurology, Emory University School of Medicine	United States	Potential conflict: Advisory board or equivalent with a commercial organization: Boehringer-Ingelheim (Blinded end-point adjudicator of cerebrovascular events in clinical trial) Potential conflict: Received payment from an organization (including gifts, other consideration, or in-kind compensation): Bayer (Blinded adjudicator of cerebrovascular end-points in clinical trial)
Jeffrey Perry	MD, MSc, CCFP-EM Professor and Vice-Chair Research/Scholarship Department of Emergency Medicine; Senior Scientist, Ottawa Hospital Research Institute; Professor Research Chair in Emergency Neurological Research University of Ottawa Emergency Physician, The Ottawa Hospital	Ontario	No conflicts to declare
Magdy Selim	MD, PhD Professor of Neurology, Harvard Medical School Chief, Division of Stroke and Cerebrovascular Disease, Beth Israel Deaconess Medical Center	United States	Potential conflict: Grant support: NIH/NINDS
Samuel Schulman	MD, PhD, FRCPS Professor of Medicine, McMaster University Director, Thrombosis Service, HHS, General Hospital, Hamilton ON, Canada Professor, Department of	Ontario	Potential conflict: Advisory board or equivalent with a commercial organization: Sanofi and Daiichi-Sankyo (Chairman of DSMB and Member of event adjudication

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
	Obstetrics and Gynecology, The First I.M. Sechenov Moscow State Medical University, Moscow, Russia		committee) Potential conflict: Research grants: Boehringer-Ingelheim and Octapharma Potential conflict: Investigator in clinical trials: Aspen; Boehringer-Ingelheim
Judy Sherman	MN NP Neurosciences Critical Care University of Alberta Hospital	Alberta	No conflicts to declare
Sean Sopher	Nurse Practitioner Stroke, Royal Alexandra Hospital	Alberta	No conflicts to declare
Catherine Varner	MD, MSc, CCFP(EM), Assistant Professor - Department of Family and Community Medicine, University of Toronto	Ontario	No conflicts to declare
Wendy Zai	MD, MPH Associate Professor Neurology, Neurosurgery, Anesthesia/Critical Care Medicine, The John Hopkins University School of Medicine, Baltimore, USA	United States	Potential conflict: Advisory board or equivalent with a commercial organization: CR Bard, Inc. (DMC) Potential conflict: Grant or an honorarium from a for-profit or not-for-profit organization: CoolTech, LLC; Vivonics, Inc (. Clinical Trial; ICP monitoring study) Potential conflict: Clinical Trial: NIH/NINDS (research support)