AHA SCIENTIFIC STATEMENT

Identifying Best Practices to Improve Evaluation and Management of In-Hospital Stroke: A Scientific Statement From the American Heart Association

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

The American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section affirms the educational benefit of this document.

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ABSTRACT: This scientific statement describes a path to optimizing care for patients who experience an in-hospital stroke. Although these patients are in a monitored environment, their evaluation and treatment are often delayed compared with patients presenting to the emergency department, contributing to higher rates of morbidity and mortality. Reducing delays and optimizing treatment for patients with in-hospital stroke could improve outcomes. This scientific statement calls for the development of hospital systems of care and targeted quality improvement for in-hospital stroke. We propose 5 core elements to optimize in-hospital stroke care:

- 1. Deliver stroke training to all hospital staff, including how to activate in-hospital stroke alerts.
- 2. Create rapid response teams with dedicated stroke training and immediate access to neurological expertise.
- 3. Standardize the evaluation of patients with potential in-hospital stroke with physical assessment and imaging.
- 4. Address barriers to treatment potentially, including interfacility transfer to advanced stroke treatment.
- Establish an in-hospital stroke quality oversight program delivering data-driven performance feedback and driving targeted quality improvement efforts. Additional research is needed to better understand how to reduce the incidence, morbidity, and mortality of in-hospital stroke.

Key Words: AHA Scientific Statements = hospitalization = inpatients = quality improvement = stroke

n-hospital stroke is defined as a stroke that occurs during a hospitalization for another diagnosis. In-hospital stroke affects between 35 000 and 75 000 hospitalized patients annually in the United States.¹ Whereas community-based strokes usually occur noniatrogenically, in-hospital stroke more commonly occurs in patients who have undergone recent procedures or invasive diagnostic testing.^{2–6} The evaluation of a patient who has recently undergone a procedure (with or without general

anesthesia) poses some unique challenges to the clinician. This includes prompt recognition and determination of whether a neurological deficit represents a new stroke or is simply a consequence of peri-procedural medications.

The advent of new therapeutic options for patients with acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) makes an accurate and timely diagnosis an important issue for in-hospital stroke. New treatment

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strategies incorporate hyperacute advanced imaging to select patients with ischemic stroke for early reperfusion therapies and have expanded the options for treating ICH, including the use of minimally invasive surgical techniques.^{7,8} All major treatments, including intravenous alteplase and mechanical thrombectomy, were developed in clinical trials that enrolled primarily patients with community-onset stroke who were first evaluated in emergency departments (EDs). The translation of these therapies to patients with in-hospital stroke has been difficult because of the added clinical complexities and the lack of standardized protocols.9,10 In addition, evidencebased guidelines and practice recommendations focus on patients presenting to the ED. This scientific statement specifically seeks to translate advances in ED acute stroke management to patients with in-hospital stroke.

METHODS

Writing group members were nominated by the committee chair and vice chair on the basis of their areas of expertise and previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council's Scientific Statement Oversight Committee and the AHA's Manuscript Oversight Committee. This process included review and minimization of relevant conflicts of interest. Participating disciplines included neurology, internal medicine, neurocritical care, neurosurgery, neurointerventional radiology, and nursing.

We performed literature searches of English-language articles related to in-hospital stroke published during 1996 to 2020 using Medline, Web of Science, and Embase. We chose 1996 as our start date because this is the year that the National Institute of Neurological Disorders and Stroke tissue plasminogen activator trial was published, ushering in the thrombolytic era. Additional focused reviews without date restrictions were conducted in PubMed, Ovid MED-LINE, Ovid Cochrane Database of Systematic Reviews, Ovid Central Register of Controlled Trials databases, Internet Stroke Center/Clinical Trials Registry,¹¹ and National Guideline Clearinghouse¹² as relevant to specific sections. The evidence was reviewed and organized within the context of the guidance from the AHA. The final manuscript was approved by the entire writing group.

EPIDEMIOLOGY

Data derived from the Stroke Data Bank (1983–1986) showed that \approx 7% of all patients with stroke had their event in the hospital.¹³ Of these strokes, 92% were ischemic and 8% were hemorrhagic. Other multihospital registries have focused specifically on AIS. In these studies, the proportion of all ischemic strokes that occur in the hospital has ranged from to 2.2% to 4.4%.¹⁴⁻¹⁷ Estimates of the proportion of all strokes that occur after hospital admission have tended to be higher in single-center studies, with

up to 17% of strokes occurring in the hospital.^{14–16,18–21} The challenge of estimating the true proportion of strokes with onset during hospitalization is that the single-center experience may not be generalizable to hospitals caring for different populations of patients or may be subject to publication bias. Generalizability is further limited when variation within the expertise and experience level of the hospital staff (academic versus nonacademic institution) is accounted for. Conversely, underreporting reinforces the lower reported proportion of in-hospital stroke in registries.

A limited amount of data confirm that the incidence of stroke among all hospitalized patients is low but that it likely varies by service. In 2008, investigators from a single center in Korea reported that 46% of ischemic stroke events occurred in the cardiology or cardiovascular services.²² The absolute rates were 0.023% for noncardiology services and 0.45% for cardiology or cardiac surgery.

No large, validated, multivariable studies have accurately classified hospitalized patients according to risk for in-hospital stroke. However, as indicated by the data on incidence, patients with a cardiovascular diagnosis are at particularly high risk.^{3,22,23} Almost half of all in-hospital stroke events occur within 24 hours of a cardiac or neurovascular procedure, including coronary artery bypass grafting, transcatheter aortic valve replacement, cerebral angiography, carotid stent, or endarterectomy.^{19,20,24,25} Vascular trauma during one of these procedures can result in dissection or disruption of atherothrombotic material. In addition, discontinuation or initiation of antithrombotic agents before, during, and after the procedure may be implicated in ischemic or hemorrhagic events, respectively. Perioperative stroke in adults undergoing cardiac and thoracic aortic operations and considerations for reducing risk are addressed in a separate scientific statement.²⁶

Some other risk factors for in-hospital stroke include infectious endocarditis, arterial dissection, acute coronary syndrome with intracardiac thrombus, dehydration, elevated hemoglobin, infection, sickle cell anemia, drug use disorder, fever, leukocytosis, elevated diastolic blood pressure, and unstable blood pressure.²⁷ A small proportion of noniatrogenic in-hospital stroke events can be attributed directly to specific causes related to the reason for admission, including rheological disorders, malignancy, or hypotension with watershed ischemia.^{9,20,25,27,29}

It is not surprising that patients with in-hospital stroke have more comorbidities, are older, and have lower premorbid functioning and more cardioembolic strokes than patients with community-onset stroke.^{2–6,23,30} Moreover, compared with patients with community-onset strokes, patients with in-hospital stroke are more likely to have a history of stroke or recent transient ischemic attack/ myocardial infarction.^{24,25,27} The older age, lower functional status, and greater burden of illness in patients with in-hospital stroke are important because they may affect the risks for treatment and calculations of the riskto-benefit ratio.

Key Points

- Roughly 2% to 4% of patients with stroke have their event during a hospitalization for another condition.
- Almost half of all in-hospital stroke events are the result of a vascular procedure.
- Risk factors for spontaneous in-hospital stroke include hemodynamic, rheologic, and inflammatory/ prothrombotic conditions associated with the acute illness.
- Discontinuation of antithrombotic medications can increase the risk of periprocedural stroke.
- Patients admitted for transient ischemic attack are at risk for in-hospital stroke.

In-Hospital Stroke Mimics

Approximately half of all in-hospital stroke alerts are ultimately determined to be a stroke mimic.^{23,31,32} In in-hospital stroke, toxic-metabolic encephalopathy, the use of sedative medications (particularly opioids and benzodiazepines), seizure, syncope, and sepsis are the most frequently encountered stroke mimics.^{9,23,32,33} In hospitalized patients, altered mental status as the sole neurological symptom is most often a stroke mimic.⁹ In contrast, other stroke mimics such as migraines, peripheral vestibulopathy, intoxication, and hypertensive crises are more common among patients in the ED.³¹

Key Points

- Suspected stroke symptoms in hospitalized patients are often nonfocal and can be confounded by medications, metabolic encephalopathy, and comorbid illness. Altered mental status without focal symptoms is more likely to be a stroke mimic.
- Commonly observed in-hospital stroke mimics are listed in Table 1.

EVALUATION

The evaluation of patients with an in-hospital stroke may be delayed or inaccurate because of obfuscating factors. For example, postprocedural dysarthria may be attributed to an anesthetic agent. Postoperative weakness may be presumed to be secondary to local pain. In addition, clinicians may wait minutes to hours to see if deficits resolve spontaneously. All of these factors can lead to delays in diagnosis and treatment.

In recognition of the importance of time, EDs conform to defined metrics to evaluate the quality of acute stroke care, and systems of care have evolved to rapidly assess and treat patients with acute stroke. These include organized response teams (eg, code stroke), standardized protocols, and the use of quality benchmarks. These are lacking in many inpatient units and may explain delays in diagnosis and management. For example, patients with in-hospital

Table 1. In-Hospital Stroke Mimics

Alteration in mental status/nonfocal impairment			
Toxic/metabolic encephalopathy			
Medication induced			
Metabolic disorders			
Respiratory disorders			
Infections/sepsis			
Dementia with acute delirium			
Hemodynamic disorders			
Hypotension			
Hypertensive emergency			
Syncope			
Somatoform disorders			
Conversion disorder			
Secondary gain			
Primary neurological disorders			
Seizure			
Tumor			
CNS infection			
Peripheral neuropathy			

CNS indicates central nervous system.

stroke have a significantly longer interval from symptom recognition to neuroimaging compared with patients with stroke in the ED setting (4.5 hours versus 1.2 hours).²¹

In our review, we identified 7 articles that provided evidence-based guidance on evaluating patients who experience in-hospital stroke.^{10,32,34–38} Recommendations included the development of formal protocols for identifying and responding to in-hospital stroke. Components of an effective protocol include (1) staff education on in-hospital stroke, (2) a simplified assessment method, (3) a defined in-hospital stroke alert activation process, and (4) a dedicated team to respond to these in-hospital stroke alerts.

Hospitals should educate members of their staff to recognize a potential stroke and empower the staff to take action (ie, activate a stroke code, stabilize the patient, begin diagnostic workup). At many hospitals, this includes all physicians, advanced practice clinicians, and nurses. Some hospitals extend this to additional staff with patient contact. Examples of individuals on the team responding to in-hospital stroke alerts include a neurologist (or other physician), an advanced practice clinician or nurse with education in stroke and neurological evaluation, stroke coordinators, pharmacy personnel, and individuals providing transport. Some hospitals may also include a respiratory therapist, a phlebotomist, or nursing aide. The involvement of the patient primary care team and prompt communication of the care plan are paramount. Telemedicine capabilities can also be used in house to evaluate patients with suspected in-hospital stroke, similar to the ED setting. This may be particularly valuable for hospitals in which neurological expertise is not immediately available to bridge the gap in health care

professional expertise, guide imaging and treatment, and recommend transfer early if deemed necessary.

Educational tools and formats include online video learning, simulation laboratories, bedside training, or a combination of the above. Recurrent education and testing should happen at regular intervals.

Recognition of stroke symptoms is paramount. The 2CAN score has 4 key risk factors that independently predict stroke. These include the clinical deficit score, akin to the Cincinnati Prehospital Stroke Score (clinical deficit score 1, 1 point; clinical deficit score ≥ 2 , 3 points), recent cardiac procedure (1 point), history of atrial fibrillation (1 point), and being a new patient (<24 hours from admission, 1 point). A score of ≥2 had a reported sensitivity of 92%, specificity of 70%, positive predictive value of 62%, and negative predictive value of 94% for identifying stroke in this retrospective, single-center study.³⁹ Although there is insufficient evidence to recommend a specific initial assessment tool, education on assessment tools and grading scores can improve in-hospital stroke recognition. Other published quality improvement projects have focused on educating inpatient staff using less complex scales (eg, Face, Arms, Speech, Time or Balance, Eyes, Face, Arm, Speech, Time).9,35,40 The National Institutes of Health Stroke Scale is a widely recognized assessment of neurological impairment severity after stroke, but it is not typically used by frontline inpatient staff as a stroke screening tool to assess neurological deficits.

Key Points

- Time from symptom onset to stroke alert is delayed in in-hospital stroke.
- Standardized protocols can reduce delays and optimize response.
- Although there is insufficient evidence to recommend a specific initial assessment tool, educating staff on the use of rapid screening tools may improve accurate evaluation of patients suspected of in-hospital stroke.
- Figure 1 outlines a stroke code response process using a defined response team within an organizational milieu that includes education, training, and feedback with data-driven oversight.

TREATMENT

Intravenous thrombolysis and endovascular treatment are evidence-based interventions for AIS. However, the AHA/American Stroke Association Get With The Guidelines registry demonstrated that the proportion of patients with in-hospital stroke treated within the first hour is lower than that of community-onset strokes (19.7% versus 29.4%), with a median of 100 minutes from symptom recognition by hospital staff to intravenous thrombolysis for patients with in-hospital stroke compared with 76 minutes from ED triage to intravenous thrombolysis for patients with community-onset strokes.¹⁵ A more recent study from the Get With The Guidelines registry evaluating trends in reperfusion therapy for patients with inhospital stroke reported higher use rates of intravenous thrombolysis (19.1% versus 9.1%) and endovascular therapy (6.4% versus 2.5%) in 2018 compared with 2008. Compared with community-onset stroke, mean times from stroke recognition to thrombolysis bolus were also prolonged at 81 minutes versus 60 minutes.¹⁷

The WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) demonstrated the utility of magnetic resonance imaging diffusion and fluid-attenuated inversion recovery mismatch in identifying patients with stroke who are eligible for intravenous thrombolytic therapy when time of symptom onset is unknown.⁴¹ Using this criterion for patient selection could potentially increase the overall treatment rate with intravenous thrombolytic by 9%.42 For high-performing centers, an even greater increase in treatment rate can be observed. Furthermore, perfusion-based imaging has also identified patients with thrombolysis treatment potential up to 9 hours from symptom onset.43,44 These imaging/ tissue-based strategies for assessing treatment eligibility may provide a unique opportunity for patients with in-hospital stroke when time of symptom onset is not clear such as those awakening from anesthesia with a focal deficit, patients with unclear documentation of baseline status, or postprocedural patients after sedation. Opportunities and barriers in obtaining acute magnetic resonance imaging in the hospital setting should be considered when developing clinical pathways for in-hospital stroke with uncertain onset time. Expansion of the therapeutic window for large vessel occlusion endovascular intervention⁷ (based on the DAWN [Diffusion-Weighted Imaging or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo] and DEFUSE-3 [Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke] data) provides treatment opportunities for in-hospital stroke that did not previously exist. Hospitals (with or without imaging capabilities) lacking endovascular expertise need to establish protocols for safe and time-efficient transfer. Engaging hospital leadership to evaluate institutional and regulatory constraints for interfacility patient transfer is critical to implementing successful protocols and minimizing delays.

The principles of management of in-hospital ICH are the same as those used for spontaneous ICH, as outlined in the AHA/American Stroke Association guideline for the management of spontaneous ICH.⁸ Initial management should include blood pressure control, typically guided by the standard ICH guidelines.⁸ Specific underlying conditions (such as hemorrhagic transformation of AIS) might require cautious blood pressure control to balance the risks of hematoma expansion and worsening ischemia; mass effect and neurological deterioration require consideration



Best Practice Processes

Bidirectional Performance Feedback Soliciting Suggestions for Improvement After Each In-Hospital Stroke Alert

Practice With Mock Stroke Alerts

(Particularly in clinical areas with less experience with stroke response)

Figure 1. A stroke code response process uses a defined response team within an organizational milieu that includes education, training, and feedback with data-driven oversight.

AC indicates accessory cephalic vein; CBC, complete blood count; HCG, human chorionic gonadotropin; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; and STAT, statim. Adapted from American Stroke Association tools acquired from the National Stroke Association and developed as part of their in-hospital stroke initiative.

for surgical intervention.⁴⁵ Reversal of anticoagulation is another mainstay of initial management and should follow standardized protocols,^{8,46} depending on the agent. Other underlying coagulopathy or thrombocytopenia should be addressed promptly with appropriate transfusion, although it may be difficult to achieve full resolution in the setting of underlying hepatic failure or renal dysfunction.

Guidance for management of ICH after thrombolysis for AIS can be found in the AHA/American Stroke Association statement on the treatment and outcome of hemorrhagic transformation after intravenous alteplase in AIS.⁴⁷ For ICH after cerebral revascularization, primarily cerebral hyperperfusion syndrome is implicated and can best be avoided with strict periprocedural blood pressure control.⁴⁸ The risks and benefits of cessation of antiplatelet therapy in the setting of ICH after these procedures must be carefully weighed. This is especially true in the setting of extracranial or intracranial stents because there is a high risk of acute stent thrombosis.

Key Points

• Patients with suspected in-hospital stroke require acute management in accordance with current

CLINICAL STATEMENTS

AND GUIDELINES

CLINICAL STATEMENTS AND GUIDELINES AHA/American Stroke Association treatment guidelines.

 Hospitals unable to provide acute stroke treatment in the inpatient setting need to engage leadership, identify key barriers, and develop the appropriate pathways to facilitate and expedite necessary transfer to a higher level of care.

OUTCOMES

Patients with in-hospital stroke have more severe stroke deficits compared with patients with community-onset strokes.¹⁵ Patients with in-hospital stroke are less likely to receive intravenous thrombolysis compared with patients in the ED as a result of delayed recognition of an acute stroke and medical contraindications such as recent surgery.^{6,21,23,31} However, they are more likely to receive comparable endovascular treatment compared with patients with community-onset strokes.^{6,31} Patient outcomes with intravenous alteplase or endovascular treatment for in-hospital stroke can be similar to those of patients with community-onset strokes.⁶

Overall, patients with in-hospital stroke experience less improvement within 24 hours, show less improvement by discharge, are less likely to be able to ambulate independently on discharge, and are less likely to return directly home.^{2,3,5,6,23,49} Analysis of the Get With The Guidelines and South London stroke registries showed that patients with in-hospital stroke were more likely to die in the hospital, and the South London registry reported a higher 5-year mortality for patients with inhospital stroke compared with patients with communityonset stroke.^{10,50}

Key Points

- Patients with in-hospital stroke have worse outcomes than patients with stroke in the community. The reasons may include increased comorbid conditions, greater stroke severity, infrequent care on stroke units, and perhaps influence of delays in care.
- Patients with in-hospital stroke receiving rapid systemic intravenous thrombolysis or endovascular therapy appear to derive benefit commensurate with strokes that occur in the community.

CHALLENGES, LIMITATIONS, AND STROKE SYSTEMS OF CARE

To expedite acute intervention for patients with in-hospital stroke, standardized training and protocols for recognizing stroke symptoms and implementing care processes homogeneously across all in-hospital services and locations are needed. There may be potential for medical personnel to incorrectly attribute new stroke symptoms in hospitalized patients to an underlying medical condition or medication. This is an area in which improved education with a variety of tools such as simulation laboratories might improve recognition and diagnosis.⁵¹

Nurses are often the first hospital staff to recognize a patient with symptoms that might indicate in-hospital stroke and activate a stroke alert. Nurses activate inhospital stroke alerts significantly earlier than physicians or advanced practice clinicians (median, 2.0 hours versus 4.9 hours) from last known well time, with median nursing activation time falling within a 3-hour window for potential systemic thrombolytic or early endovascular therapy.³⁷ Part of the reason may be that nurses are at the bedside and assess patients more frequently than other health care professionals. This supports the principle that all hospital staff should be empowered to directly activate the in-hospital stroke alert response.

Unique challenges exist for smaller hospitals that may have limited access to onsite neurological or interventional expertise. Additional challenges include less stroke education for key multidisciplinary teams and lack of multidisciplinary assessment and workflow after a stroke alert, in-hospital stroke kits for rapid intravenous thrombolysis, and standardized computerized physician order entry sets.^{10,21,30,52} Studies consistently demonstrate that community hospitals have less consistent adherence to treatment guidelines.^{2,3} Telemedicine may be beneficial in bridging the gap when medical expertise is needed, and models to enhance coverage should be explored.

In-hospital stroke can occur in hospitals lacking the resources to provide sophisticated stroke care. In such cases, it is recommended that patients be transferred to a primary or comprehensive stroke center. There are several key elements in such transfers, including recognition that a transfer is needed, communication with an accepting outside facility and health care professionals, coordination of the transfer, and execution of the transfer. Hospitals can stage mock in-hospital stroke alerts for such transfers, monitor transfer times, and use this information to perform focused quality improvement to improve performance.

Key Points

- Barriers to appropriate treatment options may include limited resources at the primary hospital.
- All hospital staff should be empowered to activate stroke alerts in the inpatient setting.
- Regional stroke systems of care should include protocols and algorithms for the transfer and treatment of patients with in-hospital stroke from spoke to hub hospitals.
- Telemedicine should be considered for in-hospital stroke code evaluation when adequate, timely expertise is unavailable.



Figure 2. Dedicated process improvement focuses on individual steps if a time interval is exceeded.

For monitoring and feedback purposes, each component of the stroke alert protocol is individually tracked and reported. IV indicates intravenous. *Reducing time from symptom onset to discovery in high-risk inpatient populations is also a valid target for quality improvement. Author consensus adapted from American Stroke Association Target: Stroke Phase III and experience with the in-hospital stroke adapted in provement initiative developed by the National Stroke Association and acquired by the American Stroke Association.

EDUCATION AND FEEDBACK

Both education and prompt feedback are essential to improve the stroke alert process. Implementation of inservice education sessions has been proven to reduce the median time from last known well to initial assessment.³⁹ Stroke education may take the form of pocket cards, posters, in-service lectures, grand rounds, and case simulation.¹⁰ Educational tools should contain information on the signs and symptoms of stroke, effect of time delays, care pathways, and roles and responsibilities of each team member. Increasing stroke awareness and adopting a more liberal approach to stroke code activation have the potential to increase the false-positive rate of stroke alerts, and the stroke program should monitor this metric.^{31,35} Feedback should be solicited after each inpatient stroke code activation and reviewed in aggregate on at least a semiannual basis in a nonpunitive and constructive fashion. This process allows continuous quality improvement.

Key Points

- Real-time feedback after each stroke code activation should be multidirectional and allow input from all individuals involved.
- For monitoring and feedback purposes, it is beneficial to track and report each component of the stroke alert protocol individually (Figure 2).

- Information should be used to refine the process and generate a culture of accountability and continuous improvement.
- Different factors that may hamper the rapid evaluation and treatment of in-hospital stroke and proposed mitigation strategies are depicted in Table 2.

TEAMS, PROCESSES, AND OVERSIGHT

Two key elements of optimal stroke care for patients with in-hospital stroke are rapid recognition and early initiation of treatment. This approach aligns well with the Target: Stroke initiative that uses best practices to improve treatment rates, times, and outcomes.⁵³ The core concepts include organizing a team to optimize the proportion of patients treated with intravenous thrombolytic within the golden hour, implementing best practice strategies to reduce door-to-needle times, using Get With The Guidelines clinical decision support tools/evidence-based strategies, and tracking progress.

Although many hospitals (especially those certified as a stroke center) will track and report care metrics for patients with AIS, such data may not routinely include the in-hospital stroke population (or may fail to discretely analyze the in-hospital stroke population). A stroke quality oversight committee should regularly review organizational performance specific to the patients with in-hospital stroke with regard to treatment times and adherence to process measures. CLINICAL STATEMENTS AND GUIDELINES

CLINICAL STATEMENTS AND GUIDELINES

Table 2.	Factors Influencing the Rapid Assessment of Hos-
pitalized	Patients With Suspected Stroke

Factor	Potential solutions				
Primary team or nurse may lack sufficient expertise in neurology	Periodic education on signs and symp- toms of stroke				
	Readily accessible information on how to activate the stroke alert				
	Case simulation				
	Scale or score adoption system				
Presence of nonfocal neurologi- cal symptoms	Adopt a liberal approach for the activa- tion of the stroke code				
	Evaluate historical data, targeted educa- tion for high-risk patient populations				
Unclear last known well or exis- tence of factors that may con- found the physical examination	Identify patients at high risk of in-hospital stroke and perform serial neurological assessments				
(eg, use of sedatives, coexisting medical conditions that may affect sensorium, intubation)	Favor the use of short-acting sedatives and hold sedatives at regular intervals to allow neurological evaluation				
Lack of familiarity with the	Develop checklists				
stroke protocol or inconsis- tent adherence to the stroke	Periodic education on stroke alert pro- cess, including roles and responsibilities				
protocol	Real-time feedback to stakeholders				
Health care professionals may be uncertain of what tests to order	Develop in-hospital stroke-dedicated protocols and order sets				
Delays in transportation and imaging	Adopt clear time goals for CT comple- tion and reported results				
	Develop a rapid transportation protocol				
Inconsistent adherence to stroke QI metrics	Monitor the use of stroke order sets for in-hospital strokes				
	Review metrics and establish bench- marking for the in-hospital stroke response team				

CT indicates computed tomography; and QI, quality improvement.

The care team that responds to in-hospital stroke might be the same stroke code team that responds to all stroke alerts. Some organizations might consider delegating this to a separate rapid response team that manages patients with nonspecific medical emergencies. Hospitals with higher volumes of stroke alerts may elect to use a dedicated stroke code team for both the ED and in-hospital setting.

There are insufficient data to inform an evidencebased recommendation on the composition or design of in-hospital stroke response teams across all settings. Written hospital protocols defining processes and responsibilities should be established in accordance to AHA guidelines and hospital policy. Reviewing metrics such as the number of in-hospital stroke alerts, true stroke rates with subtypes, response times, imaging acquisition times, treatment rates, treatment times, and outcomes will support quality improvement and identify potential barriers and opportunities.

Key Point

• Institutions should develop a plan for in-patient stroke response teams that includes education, quality review, and specified oversight (Figure 1).

CALL FOR ONGOING QUALITY IMPROVEMENT AND TRACKING

Optimizing response time and health care resource stewardship and improving adherence to consensus quality measures are key areas of emphasis for quality improvement. Efforts to increase the recognition and timely treatment of in-hospital stroke need to be balanced by measures that ensure that stroke codes are used appropriately. Larger studies such as those that have examined in-hospital myocardial infarctions and compared them with matched controls are needed to establish risk factors, treatment rates, mortality, and outcomes relative to strokes in patients presenting to the ED.⁵⁴

Key Point

• Focused efforts are needed to improve adherence to consensus quality metrics for in-hospital stroke.

DISCUSSION

The following key components should be in place to optimize the evaluation and management of in-hospital stroke:

- Education: Ongoing stroke education for all hospital staff should include recognition of stroke symptoms and how to activate a stroke alert.
- In-hospital stroke teams: Response teams should include members trained to homogeneously care for patients with stroke.
- Process and protocols: Written protocols are recommended to expedite treatment and ensure consistency. Necessary resources may include expedited transport, access to rapid imaging, thrombolytic drug availability, and staffing capable of rapidly delivering medical/endovascular/surgical treatment at any time.
- Challenges, barriers, and limitations: Key barriers within the hospital or health care system should be identified and addressed, and a pathway for interfacility patient transfer should be established when appropriate.
- Quality improvement: In-hospital stroke performance and quality data should be examined specifically and used to drive focused quality improvement efforts. Reporting all in-hospital stroke cases to a registry may help with monitoring the true incidence of in-hospital stroke and provide data for future research.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on March 4, 2021, and the American Heart Association Executive Committee on April 22, 2021. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

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Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition. "Modest.

Reviewer Disclosures

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Sean Ruland	Loyola University Health System	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

REFERENCES

- 1. Cumbler E. In-hospital ischemic stroke. *Neurohospitalist.* 2015;5:173–181. doi: 10.1177/1941874415588319
- Moradiya Y, Levine SR. Comparison of short-term outcomes of thrombolysis for in-hospital stroke and out-of-hospital stroke in United States. *Stroke.* 2013;44:1903–1908. doi: 10.1161/STROKEAHA. 113.000945
- Schürmann K, Nikoubashman O, Falkenburger B, Tauber SC, Wiesmann M, Schulz JB, Reich A. Risk profile and treatment options of acute

ischemic in-hospital stroke. *J Neurol.* 2016;263:550–557. doi: 10.1007/s00415-015-8010-2

- Yoo J, Song D, Baek JH, Lee K, Jung Y, Cho HJ, Yang JH, Cho HJ, Choi HY, Kim YD, et al. Comprehensive code stroke program to reduce reperfusion delay for in-hospital stroke patients. *Int J Stroke.* 2016;11:656–662. doi: 10.1177/1747493016641724
- Caparros F, Ferrigno M, Decourcelle A, Hochart A, Moulin S, Dequatre N, Bodenant M, Hénon H, Cordonnier C, Leys D. In-hospital ischaemic stroke treated with intravenous thrombolysis or mechanical thrombectomy. *J Neurol.* 2017;264:1804–1810. doi: 10.1007/s00415-017-8570-4

- Lu MY, Chen CH, Yeh SJ, Tsai LK, Lee CW, Tang SC, Jeng JS. Comparison between in-hospital stroke and community-onset stroke treated with endovascular thrombectomy. *PLoS One.* 2019;14:e0214883. doi: 10.1371/journal.pone.0214883
- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2019;50:e440-e441]. *Stroke*. 2019;50:e344-e418. doi: 10.1161/STR.000000000000211
- Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2015;46:2032–2060. doi: 10.1161/STR.00000000000069
- El Husseini N, Goldstein LB. "Code stroke": hospitalized versus emergency department patients. J Stroke Cerebrovasc Dis. 2013;22:345–348. doi: 10.1016/j.jstrokecerebrovasdis.2011.09.012
- Cumbler E, Zaemisch R, Graves A, Brega K, Jones W. Improving stroke alert response time: applying quality improvement methodology to the inpatient neurologic emergency. *J Hosp Med.* 2012;7:137–141. doi: 10.1002/jhm.984
- 11. Stroke Center. Accessed November 26, 2019. http://www.strokecenter. org/trials
- 12. Agency for Healthcare Research and Quality. Guidelines and measures. Accessed November 26, 2019. http://guideline.gov/
- Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. *Stroke*. 1988;19:547–554. doi: 10.1161/01.str.19.5.547
- Cumbler E, Murphy P, Jones WJ, Wald HL, Kutner JS, Smith DB. Quality of care for in-hospital stroke: analysis of a statewide registry. *Stroke*. 2011;42:207–210. doi: 10.1161/STROKEAHA.110.590265
- Cumbler E, Wald H, Bhatt DL, Cox M, Xian Y, Reeves M, Smith EE, Schwamm L, Fonarow GC. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines–Stroke. *Stroke*. 2014;45:231–238. doi: 10.1161/STROKEAHA.113.003617
- Kimura K, Minematsu K, Yamaguchi T. Characteristics of in-hospital onset ischemic stroke. *Eur Neurol.* 2006;55:155–159. doi: 10.1159/000093574
- Akbik F, Xu H, Xian Y, Shah S, Smith EE, Bhatt DL, Matsouaka RA, Fonarow GC, Schwamm LH. Trends in reperfusion therapy for in-hospital ischemic stroke in the endovascular therapy era. *JAMA Neurol.* 2020;77:1486– 1495. doi: 10.1001/jamaneurol.2020.3362
- Dulli D, Samaniego EA. Inpatient and community ischemic strokes in a university hospital. *Neuroepidemiology*. 2007;28:86–92. doi: 10.1159/000098551
- Kelley RE, Kovacs AG. Mechanism of in-hospital cerebral ischemia. *Stroke*. 1986;17:430–433. doi: 10.1161/01.str.17.3.430
- Farooq MU, Reeves MJ, Gargano J, Wehner S, Hickenbottom S, Majid A; Paul Coverdell National Acute Stroke Registry Michigan Prototype Investigators. In-hospital stroke in a statewide stroke registry. *Cerebrovasc Dis.* 2008;25:12–20. doi: 10.1159/000111494
- Saltman AP, Silver FL, Fang J, Stamplecoski M, Kapral MK. Care and outcomes of patients with in-hospital stroke. *JAMA Neurol.* 2015;72:749–755. doi: 10.1001/jamaneurol.2015.0284
- Park HJ, Cho HJ, Kim YD, Lee DW, Choi HY, Kim SM, Heo JH. Comparison of the characteristics for in-hospital and out-of-hospital ischaemic strokes. *Eur J Neurol.* 2009;16:582–588. doi: 10.1111/j.1468-1331. 2009.02538.x
- Topiwala K, Tarasaria K, Staff I, Beland D, Schuyler E, Nouh A. Identifying gaps and missed opportunities for intravenous thrombolytic treatment of inpatient stroke. *Front Neurol.* 2020;11:134. doi: 10.3389/fneur.2020.00134
- Azzimondi G, Nonino F, Fiorani L, Vignatelli L, Stracciari A, Pazzaglia P, D'Alessandro R. Incidence of stroke among inpatients in a large Italian hospital. *Stroke*. 1994;25:1752–1754. doi: 10.1161/01.str.25.9.1752
- Vera R, Lago A, Fuentes B, Gállego J, Tejada J, Casado I, Purroy F, Delgado P, Simal P, Martí-Fábregas J, et al; Stroke Project of the Spanish Cerebrovascular Diseases Study Group. In-hospital stroke: a multicentre prospective registry. *Eur J Neurol.* 2011;18:170–176. doi: 10.1111/j.1468-1331.2010.03105.x

- 26. Gaudino M, Benesch C, Bakaeen F, DeAnda A, Fremes SE, Glance L, Messé SR, Pandey A, Rong LQ; on behalf of the American Heart Association Council on Cardiovascular Surgery and Anesthesia; Stroke Council; and Council on Cardiovascular and Stroke Nursing. Considerations for reduction of risk of perioperative stroke in adult patients undergoing cardiac and thoracic aortic operations: a scientific statement from the American Heart Association. *Circulation.* 2020;142:e193–e209. doi: 10.1161/CIR.000000000000885
- Nadav L, Gur AY, Korczyn AD, Bornstein NM. Stroke in hospitalized patients: are there special risk factors? *Cerebrovasc Dis.* 2002;13:127–131. doi: 10.1159/000047762
- 28. Deleted in proof.
- Spencer FA, Gore JM, Yarzebski J, Lessard D, Jackson EA, Goldberg RJ. Trends (1986 to 1999) in the incidence and outcomes of in-hospital stroke complicating acute myocardial infarction (the Worcester Heart Attack Study). *Am J Cardiol.* 2003;92:383–388. doi: 10.1016/s0002-9149(03) 00654-4
- Koge J, Matsumoto S, Nakahara I, Ishii A, Hatano T, Sadamasa N, Kai Y, Ando M, Saka M, Chihara H, et al. Improving treatment times for patients with in-hospital stroke using a standardized protocol. *J Neurol Sci.* 2017;381:68–73. doi: 10.1016/j.jns.2017.08.023
- Del Brutto VJ, Ardelt A, Loggini A, Bulwa Z, El-Ammar F, Martinez RC, Brorson J, Goldenberg F. Clinical characteristics and emergent therapeutic interventions in patients evaluated through the in-hospital stroke alert protocol. *J Stroke Cerebrovasc Dis.* 2019;28:1362–1370. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.001
- Cumbler E, Simpson J. Code stroke: multicenter experience with in-hospital stroke alerts. J Hosp Med. 2015;10:179–183. doi: 10.1002/jhm.2311
- Natteru P, Mohebbi MR, George P, Wisco D, Gebel J, Newey CR. Variables that best differentiate in-patient acute stroke from stroke-mimics with acute neurological deficits. *Stroke Res Treat.* 2016;2016:4393127. doi: 10.1155/2016/4393127
- Bunch ME, Nunziato EC, Labovitz DL. Barriers to the use of intravenous tissue plasminogen activator for in-hospital strokes. J Stroke Cerebrovasc Dis. 2012;21:808–811. doi: 10.1016/j. jstrokecerebrovasdis.2011.04.012
- Cumbler E, Anderson T, Neumann R, Jones WJ, Brega K. Stroke alert program improves recognition and evaluation time of in-hospital ischemic stroke. J Stroke Cerebrovasc Dis. 2010;19:494–496. doi: 10.1016/j.jstrokecerebrovasdis.2009.09.007
- Garcia-Santibanez R, Liang J, Walker A, Matos-Diaz I, Kahkeshani K, Boniece I. Comparison of stroke codes in the emergency room and inpatient setting. *J Stroke Cerebrovasc Dis.* 2015;24:1948–1950. doi: 10.1016/j.jstrokecerebrovasdis.2015.05.010
- George P, Wisco DR, Gebel J, Uchino K, Newey CR. Nurses are as specific and are earlier in calling in-hospital stroke alerts compared to physicians. J Stroke Cerebrovasc Dis. 2017;26:917–921. doi: 10.1016/j. jstrokecerebrovasdis.2016.10.003
- Kassardjian CD, Willems JD, Skrabka K, Nisenbaum R, Barnaby J, Kostyrko P, Selchen D, Saposnik G. In-patient code stroke: a quality improvement strategy to overcome knowledge-to-action gaps in response time. *Stroke.* 2017;48:2176–2183. doi: 10.1161/STROKEAHA.117.017622
- Chang P, Ruff I, Mendelson SJ, Caprio F, Bergman DL, Prabhakaran S. The 2CAN score: development of a novel inpatient stroke detection tool. *Stroke*. 2018;49:2866–2871. doi: 10.1161/STROKEAHA.118.022130
- El Ammar F, Ardelt A, Del Brutto VJ, Loggini A, Bulwa Z, Martinez RC, McKoy CJ, Brorson J, Mansour A, Goldenberg FD. BE-FAST: a sensitive screening tool to identify in-hospital acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2020;29:104821. doi: 10.1016/j. jstrokecerebrovasdis.2020.104821
- Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al; WAKE-UP Investigators. MRI-guided thrombolysis for stroke with unknown time of onset. N Engl J Med. 2018;379:611–622. doi: 10.1056/NEJMoa1804355
- 42. Silver B, Arnold M. Implications of the WAKE-UP trial. *Stroke.* 2018;49:3115–3117. doi: 10.1161/STROKEAHA.118.022436
- Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med. 2019;380:1795–1803. doi: 10.1056/ NEJMoa1813046
- 44. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, et al; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4:5-9 h and wake-up stroke using perfusion imaging: a systematic review and

meta-analysis of individual patient data. *Lancet*. 2019;394:139-147. doi: 10.1016/S0140-6736(19)31053-0

- Hanley DF, Li Y. Invited editorial commentary: more than one way to treat the mass effect. *Neurocrit Care.* 2020;32:363–364. doi: 10.1007/ s12028-019-00851-z
- 46. Frontera JA, Lewin JJ 3rd, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care.* 2016;24:6–46. doi: 10.1007/s12028-015-0222-x
- 47. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, Kim LJ, Mayer SA, Sheth KN, Schwamm LH; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2017;48:e343–e361. doi: 10.1161/STR.000000000000152
- Carvalho AM, Nzwalo H. Intracerebral hemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization: systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2017;159:2089– 2097. doi: 10.1007/s00701-017-3328-4

- Mönch S, Lehm M, Maegerlein C, Hedderich D, Berndt M, Boeckh-Behrens T, Wunderlich S, Kreiser K, Zimmer C, Friedrich B. Worse endovascular mechanical recanalization results for patients with in-hospital onset acute ischemic stroke. *J Neurol.* 2018;265:2525–2530. doi: 10.1007/s00415-018-9035-0
- Emmett ES, Douiri A, Marshall IJ, Wolfe CDA, Rudd AG, Bhalla A. A comparison of trends in stroke care and outcomes between in-hospital and community-onset stroke: the South London Stroke Register. *PLoS One.* 2019;14:e0212396. doi: 10.1371/journal.pone.0212396

CLINICAL STATEMENTS

AND GUIDELINES

- Ortega J, Gonzalez JM, de Tantillo L, Gattamorta K. Implementation of an in-hospital stroke simulation protocol. Int J Health Care Qual Assur. 2018;31:552–562. doi: 10.1108/IJHCQA-08-2017-0149
- Manners J, Khandker N, Barron A, Aziz Y, Desai SM, Morrow B, Delfyett WT, Martin-Gill C, Shutter L, Jovin TG, et al. An interdisciplinary approach to inhospital stroke improves stroke detection and treatment time. *J Neurointerv Surg.* 2019;11:1080–1084. doi: 10.1136/neurintsurg-2019-014890
- Fonarow GC, Xin Zhao MS, Smith EE, Bhatt DL, Ying Xian MD, Hernandez AF, Peterson ED, Schwamm LH. Improving door-to-needle times in acute ischemic stroke: principal results from the Target: Stroke initiative. *JAMA*. 2014;311:1632-1640.
- Bradley SM, Borgerding JA, Wood GB, Maynard C, Fihn SD. Incidence, risk factors, and outcomes associated with in-hospital acute myocardial infarction. *JAMA Netw Open.* 2019;2:e187348. doi: 10.1001/ jamanetworkopen.2018.7348

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