AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- DISTINGUISH types of stroke by presentation to determine appropriate treatment
- LIST proper dosage, administration, and monitoring knowledge for the healthcare team
- GIVE providers and patients the most up to date evidence-based medicine
- DEMONSTRATE ability to manage community-based post-stroke patients safe and effectively

After participating in this activity pharmacy technicians will be able to:

- DISCUSS the basic facts about stroke
- RECOGNIZE the signs of stroke and refer patients to emergency care
- LIST ways to encourage stroke patients to adhere to medication regimens and healthy lifestyles
- IDENTIFY when patients require pharmacist counseling

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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Acting with Expediency: Medication as the Cornerstone of Stroke Prevention and Treatment

ABSTRACT: A stroke occurs when the brain receives insufficient oxygen due to infarction or hemorrhage. Despite research advances in stroke prevention and management, someone in the United States suffers a stroke about every 40 seconds and dies from stroke every four minutes.[1] It is unclear why there are disparities in stroke mortality among geographic regions and racial/ethnic groups. Furthermore, stroke is a leading cause of serious long-term disability in our nation and causes enormous suffering among survivors. Correspondingly, total direct and indirect costs of cardiovascular disease and stroke exceed $350 billion a year in the U.S.[1] Optimal stroke care requires urgent recognition of symptoms, timely initiation of appropriate treatment to all eligible patients, and appropriate secondary prevention measures.

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INTRODUCTION

Hippocrates created the term apoplexy to describe a disorder where "a person suddenly falls, without consciousness or motion, retaining pulse and respiration."[2] The advent of autopsies during the Modern Era and rapid scientific and technological advancements from the 17th century onward led to the modern definition of stroke, which ultimately replaced apoplexy in the literature.[2] A universally accepted definition of stroke is a sudden loss of brain function caused by interrupted blood flow (ischemic) or rupture of a brain blood vessel (hemorrhagic).[2,3] Stroke's variable definition among reputable sources poses a challenge for providers in clinical practice and for epidemiologists to create accurate and comparable population-based data.[4] The World Health Organization (WHO) definition of stoke is "rapidly developing clinical signs of focal [or global] disturbance of cerebral function, lasting more than 24 hours or leading to death,

with vascular origin."[4] WHO defines transient ischemic attack (TIA or a mini-stroke) as "sudden onset of focal neurological symptoms and signs lasting less than 24 hours and caused by reversible cerebral ischemia."[4]

Advances in basic science, neuroimaging, diagnostic techniques, and acute stroke management call for reconsideration of criteria to define stroke.[4] Evidence that permanent injury can occur before the 24-hour threshold makes these purely time-based definitions obsolete. Therefore, the American Heart Association and the American Stroke Association (AHA/ASA) jointly released an expert consensus document, "An Updated Definition of Stroke for the 21st Century" that incorporates both clinical and tissue criteria to define stroke and TIA.[5] A similar definition appears in the WHO's upcoming *International Classification of Disease* (ICD-11), but subtle differences may impact population-based studies and clinical care recommendations.[4]

Potential for Major Revolution in Outcomes

Stroke is preventable, treatable, and beatable. In situations where lack of or conflicting evidence limits decision making, the healthcare team must collaborate and consider patients case by case. Healthcare professionals including paramedics, nurses, radiologists, neurologists, and pharmacists must join forces to provide coordinated stroke prevention and care. Early recognition, access to care, and timely initiation of treatment to all eligible patients are essential to reduce stroke's global burden. Knowledgeable pharmacists lead by example, promote patient and medical team education and behavior change, and achieve all around better outcomes.

Shockingly, about 80% of strokes are preventable.[8] Yet the vascular event still kills approximately 129,000 Americans annually, ranking fifth among all causes of death in the U.S.[1,9] Although the number of stroke deaths per 100,000 population fell from a baseline of 43.5 in 2007 to 37.6 in 2017, we still didn't reach the national goal of 34.8. Experts predict stroke death rates will continue to decline, but likely at a slower rate. Tracking seven key health factors and behaviors that increase risks for heart disease and stroke can help fulfill the Healthy People 2020 objective, a 20% decline in the stroke death rate over the decade. "Life's Simple 7" are smoking cessation, physical activity, healthy diet, healthy body weight, and control of cholesterol, blood pressure, and blood sugar.[1]

Furthermore, despite declines in stroke mortality rates in the U.S., the global burden of stroke is increasing.[4] In 2013, 31% of all global deaths were of cardiovascular origin, and 80% of those deaths took place in low- and middle-income countries.[1] The WHO Global Action Plan for the Prevention and Control of noncommunicable diseases (NCDs) aims for a 25% relative reduction in the overall mortality from cardiovascular disease, cancer, diabetes, or chronic respiratory disease.[10]

PAUSE AND PONDER: Can you list the signs and symptoms of stroke or differentiate between stroke and a transient ischemic attack?

Advancements in scientific research and technology provide opportunity to shift the paradigm from nationwide stroke burden reduction to world-wide. Stroke registries document the role of systems-level approaches to maximize quality-of-care indicators and improve patient outcomes.[11] Two active national stroke registries exist, the AHA Get With The Guidelines-Stroke (GWTG-S) and the Centers for Disease Control and Prevention (CDC)-funded Paul Coverdell National Acute Stroke Registry. GWTG-S tracks hospital compliance with current evidence based care and helps determine impact of acute stroke therapies on patient outcomes.[11] Leveraging available tools can help prevent, treat, and reduce stroke's long-term impact and track progress towards national and global goals.

Acute Stroke Urgency: Seconds Count

Stroke patient outcomes depend on factors including urgent symptom recognition, immediate access to care, prompt diagnosis, and timely treatment initiation.[12] Seamless coordination among partners in the stroke chain of survival like emergency medical services (EMS), certified stroke centers, and rehabilitation services, support a successful stroke system of care.[13] Strokes have varying causes, distinct classifications, and manifest many effects. All members of the medical team must be able to recognize stroke's signs and symptoms and be prepared to react urgently.

Clinicians cannot diagnose the type of stroke based on symptom presentation only. There are common symptoms between the major types of stroke, but the distinct pathophysiologic differences are usually visible with brain imaging. Regardless of the type of stroke, time is critical, even after symptoms resolve (i.e., TIA). The EXPRESS trial (Early use of eXisting PREventive Strategies for Stroke) found 8.2% absolute risk reduction for recurrent stroke within 90 days in TIA patients with urgent assessment and treatment. Diagnostic work-up in this study included brain and vascular imaging along with an EKG. **Table 1** shows the major types of stroke and the common symptoms.[12]

Table 1. Type of Stroke and Symptom Overview[12]

Type of Stroke	Symptoms
Ischemic (Clots)	One sided facial droop, one arm drifts down when raising both, sudden slurred speech, confusion, difficulty walking, loss of coordination, severe headache and/or difficulty seeing in one or both eyes
Hemorrhagic (Bleeds)	
TIA (Transient Ischemic Attack)	Temporary symptoms (as above), only present for a short period of time and completely resolves

The CDC analyzed survey data from the 2005 Behavior Risk Factor Surveillance System (BRFSS) to assess public awareness of stroke warning symptoms and the importance of seeking emergency care.[7] Only 16.4% of respondents met all three of these measures:

1. Recognize all five stroke symptoms
2. Identify an incorrect symptom
3. Recognize the need to call 911

The majority of respondents recognized sudden numbness or weakness especially on one side, confusion or trouble speaking, walking or loss of balance, visual deficits, and severe headache as stroke warning symptoms. However, 39.5% of respondents incorrectly identified chest pain as a stroke warning symptom, which is more often associated with an acute myocardial infarction (MI) or heart attack.[7] Although acute MI and stroke share common risk factors and primary prevention measures, they are very different. Stroke is sometimes called a "brain attack."[5,13] Interestingly, the least recognized individual stroke symptom in the BRFSS survey was sudden severe headache (76%).[7]

Stroke has heterogenous origins that includes cerebral hemorrhage and several pathogenic ischemic stroke subtypes (atherosclerotic, cardioembolic, lacunar, others).[14] Acute ischemic stroke (AIS) accounts for about 87% of all strokes in the U.S.[15] Nevertheless, patients experiencing hemorrhagic stroke often feel more ill and describe the worst headache of their life, sometimes rendering them unconscious.[13] About one-third of hemorrhagic stroke patients die within 30 days, demonstrating that hemorrhagic stroke is more fatal than AIS.[1,16]

BRFSS respondent awareness of stroke warning symptoms and those more likely to call 911 varied by race/ethnicity, sex, and education level. The populations most aware of stroke warning symptoms were white, women, and people with higher education.[7] Available evidence for prehospital stroke management suggests targeting public awareness interventions in populations with lower stroke awareness and those at increased risk of prehospital delays in seeking care.[12] While only about 60% of all stroke patients use EMS, men, Black, and Hispanic populations are even less likely to call 911.[12] Urgent access to EMS care for all patients is associated with the following[12]:

- Earlier ED arrival symptom onset-to-ED door time of three hours or fewer
- Quicker ED evaluation (more patients with door-to-imaging time of 25 minutes or fewer)
- More rapid mechanical (thrombectomy) or thrombolytic treatment (more patients with door-to-needle [DTN] time less than 60 minutes)
- More eligible patients being treated with alteplase if onset is two hours or fewer

Updated guideline recommendations broaden the target audience to include the public, physicians, hospital personnel, and EMS in hopes of raising stroke urgency awareness.[12] Public and healthcare personnel must recognize stroke symptoms and call 911 immediately to access urgent care. The acronym FAST (face drooping, arm weakness, speech difficulty, time to call 911) is an easy way to remember the most common signs of AIS and how to respond. Educated patients, caregivers, and healthcare providers may increase 911 use, decrease stroke onset to ED arrival times, and increase timely use of thrombolysis and thrombectomy.[12]

AHA GWTG-S simplifies EMS response to stroke in three easy steps 1) Assess, 2) Alert, 3) Arrive.[13]

1. Assess Stroke Patient

Upon arrival at the scene, EMS personnel first support the ABCs: **A**irway, **B**reathing, and **C**irculation. EMTs then use several different prehospital stroke scales to evaluate the patient and estimate the severity of potential stroke. The Cincinnati Prehospital Stroke Scale evaluates three parameters: facial droop, arm drift, and speech. The Los Angeles Prehospital Stroke Screen (LAPSS) expands on the Cincinnati Prehospital Stroke Scale and includes screening criteria (i.e., age over 45 years, history of seizure, onset of neurologic symptoms in last 24 hours, blood glucose). Guidelines for the management of AIS recommend using the National Institutes of Health Stroke Scale (NIHSS) during emergency evaluation.[12] The NIHSS is a 15-item neurologic examination to evaluate acute cerebral infarction's effect on consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. System wide use of well-validated national stroke scales like the NIHSS allows better comparability between studies.[12]

Stroke scales quantify the degree of neurologic deficit and provide objective measurement of changing clinical status.[12] Stroke scales can also help identify candidates for fibrinolytic or mechanical intervention and those at high risk for complications like intracerebral hemorrhage (ICH).[12] Reperfusion with alteplase, a recombinant tissue plasminogen activator (tPA), remains the gold standard treatment for AIS.[17] For patients with large vessel occlusions in whom pharmacological thrombolysis is contraindicated or ineffective, mechanical endovascular thrombectomy is a treatment option.[18] Mechanical endovascular reperfusion therapy to physically remove a blood clot comprises a number of mechanical procedures and medical devices.[18] Availability to this relatively new technique is contingent on access to trained interventionalists and necessary equipment.[18] Both alteplase and mechanical thrombectomy have specific treatment eligibility criteria that depends on the

patient's Last Known Well (LKW) time, so questioning the patient, a family member, or anyone else with the patient is important.

Furthermore, baseline stroke severity as measured by the NIHSS strongly influences stroke outcome measures. Older age, elevated blood glucose, and infarct on imaging are other predictors of poor outcomes.[12] Establishing time of symptom onset and checking blood glucose are key to initial assessment. Also, in some cases hypoglycemia can mimic stroke symptoms, so EMS personnel should always rule this out. All patients must receive a blood glucose assessment before the initiation of IV alteplase.[12] Other differential diagnoses to consider include seizure, medication effect, toxin exposure, electrolyte abnormalities, concussion/trauma, and infection.

2. Alert the Receiving Certified Stroke Facility

The Brain Attack Coalition, national leaders in stroke care, advise EMS drivers to transport suspected stroke patients to the nearest stroke-certified facility (even if this means bypassing other hospitals).[13] While most hospitals can provide basic stroke care, a stroke-certified or -designated hospital delivers stroke care according to national recommendations.[13] Some qualifications for hospital certification include [13]

- ability to perform CT scans 24/7
- IV alteplase available 24/7
- neurosurgical consults attainable within 15 minutes

In the AHA GWTG registry, EMS prearrival notification to the destination ED increased likelihood of alteplase treatment within three hours, and shortened door-to-imaging, door-to-needle, and symptom onset-to-needle times.[12]

3. Arrive at a Certified or Designated Stroke Center

Upon arrival to care, immediate clinical assessment (e.g., history, physical exam, laboratory tests) and neurological assessment using stroke scales such as NIHSS, help determine stroke severity and guide treatment. Various techniques help clinicians diagnose stroke, like infarct or hemorrhage based on imaging, or TIA established by negative imaging and symptom resolution within 24 hours from onset.[5] Inaccuracies in stroke diagnosis or medication selection can lead to major adverse events like hemorrhage and death. The immediate goal of stroke treatment is restoration of blood flow to the brain to obtain complete neurologic recovery.[12] Depending on the type of stroke, treatment may involve reperfusion therapy with a thrombolytic agent, a clot-removing medical procedure, or an alternative therapy. The majority of acute stroke patients do not require urgent anticoagulation (e.g., heparin drip). Prior to neuroimaging and differentiation of ischemic from hemorrhagic stroke, clinicians must not administer any medication, not even aspirin.[12]

Prior to IV alteplase initiation, patients require braining imaging studies to rule out hemorrhage. Reducing the time interval from ED presentation to initial brain imaging can help reduce time to treatment initiation.[12] The medical team should aim to obtain brain imaging within 20 minutes of arrival in at least 50% of stroke patients who may be candidates for IV alteplase or mechanical thrombectomy.

Telemedicine enhances real-time access to state-of-the-art management of patients with acute cerebrovascular syndromes.[5] FDA-approved teleradiology systems can read brain images and effectively support rapid imaging interpretation.[12] Telemedicine/telestroke is especially useful in rural areas or other regions with limited access to certified stroke facilities and other resources.[12]

PAUSE AND PONDER: Where are the stroke-certified facilities closest to your pharmacy and your home?

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Optimize Clot-Busting IV Alteplase

A thrombus (blood clot) is the most common cause of stroke, often occluding the middle cerebral artery, the largest branch of the internal carotid artery.[9] A thrombus stuck in a blood vessel blocks oxygen transportation to vital brain areas including the frontal, temporal, and parietal lobes. About 1.9 million neurons die every minute without oxygen.[13] Other AIS sources include clots that travel to the brain from the left atria (atrial fibrillation) or ventricle (severe heart failure), or plaque (fatty deposits and cholesterol) accumulation that clogs blood vessels.[13]

Alteplase binds to fibrin in a thrombus (clot) and converts plasminogen to plasmin, which causes fibrinolysis. The phrase "time is brain" refers to the urgent need to reperfuse the brain when stroke symptoms occur in order to maximize time-dependent treatment outcomes. Pooled results from randomized controlled trials (RCTs) along with registry data from AHA GWTG-S confirm alteplase's benefit is greatest when treatment occurs early after stroke onset. Its benefits decline with time.[12,17,19-21] Alteplase is most effective when symptom onset is within three hours of administration (and up to four and a half hours in certain eligible patients). Eligibility criteria for IV alteplase administration is complex, so clinicians should consider each patient individually and comprehensively. Most importantly, clinicians must exclude intracranial hemorrhage before administering IV alteplase. Other tests (i.e., international normalized ratio, activated partial thromboplastin time, platelet count) may be beneficial in some patients. However, if there is no reason to suspect abnormal results, treatment should not be delayed awaiting hematologic or coagulation results.[12]

Alteplase is contraindicated when bleeding risk exceeds potential benefit. Some exclusion criteria include active internal bleeding; recent intracranial or intraspinal surgery or serious head trauma; intracranial conditions that may increase bleeding risk; current intracranial or subarachnoid hemorrhage; and current severe uncontrolled hypertension.

Four and one-half hours after symptom onset, deleterious effects ensue, including hemorrhagic transformation (HT), which causes the most significant morbidity and mortality in stroke patients.[12,17,19-21] Despite data clearly proving time-dependent alteplase benefits, less than 30% of U.S. patients are treated within the recommended window.[12,13] Due to treatment delays, about 15% to 30% of stroke survivors experience long-term moderate to severe disability.[13]

The updated 2019 AIS Guidelines recommendations expand telemedicine's role in facilitating alteplase eligibility decision making and triaging patients.[12] The STRokED DOC (Stroke Team Remote Evaluation Using a Digital Observation Camera) pooled analysis supported use of telemedicine consultations, including teleradiology, for more accurate IV alteplase eligibility decision making in the ED.[12] Other strategies to enhance the therapeutic time window for alteplase therapy that simultaneously reduce the risk of adverse effects (especially HT) remain an unmet clinical need.[17] Although some pharmacologic agents show promising results in reducing delayed alteplase-induced HT, their long term efficacy in terms of preserving neurovascular function is still uncertain.[17] Researchers continue to study agents that putatively preserve the blood-brain barrier (e.g., minocycline, cilostazol, fasudil, candesartan, and bryostatin), and/or enhance vascularize-

tion and protect the cerebrovascular function (e.g., coumarin derivatives and granulocyte colony-stimulating factor).[17] As researchers work to develop therapeutic breakthroughs, healthcare teams must base treatment decisions on the strongest and most applicable current clinical evidence.

Patient factors most strongly associated with shorter onset-to-treatment times include greater stroke severity, arrival by ambulance, and arrival during regular hours.[12, 22] To guide healthcare providers, the AHA/ASA launched a national quality improvement initiative to reduce door-to-needle times (DTN) for patients eligible for alteplase. The goal is a DTN time of 60 minutes or fewer in more than 50% of stroke patients treated with IV alteplase.[12] In an analysis of 58,353 alteplase-treated patients, treatment started more rapidly (evaluated in 15-minute increments) was associated with several benefits [12, 22]:

- reduced in-hospital mortality (OR, 0.96 [95% CI, 0.95–0.98]; P<0.001),
- reduced symptomatic intracerebral hemorrhage (OR, 0.96 [95% CI, 0.95–0.98]; P<0.001),
- increased independent ambulation at discharge (OR, 1.04 [95% CI, 1.03–1.05]; P<0.001), and
- increased discharge to home (OR, 1.03 [95% CI, 1.02–1.04]; P<0.001) .

In addition to timely treatment initiation, proper alteplase administration requires accurate dosing, reconstitution, close monitoring, and follow up. The Health Grades Inc Patient Safety in American Hospitals study examined 37 million patient records and estimated 195,000 Medicare patients die due to preventable in-hospital medical errors annually.[3,23] A retrospective chart review from 234 ischemic and hemorrhagic stroke cases revealed a 19% in-hospital incidence rate of medication errors.[17] The most common errors linked to IV alteplase were underuse and misuse (i.e., dosing errors, patient selection, and timing).[17]

Other preventable medication errors occur with use of abbreviations like “tPA” that can be easily mistaken for “TNK.” Providers may use “tPA” to refer to Activase (generic alteplase), because it was the first tissue plasminogen activator approved. Alteplase is indicated for acute myocardial infarction, acute ischemic stroke, and acute massive pulmonary embolism. The Food and Drug Administration (FDA) has only approved other tissue plasminogen activators—Retavase (generic reteplase) and TNKase (generic tenecteplase)— for acute myocardial infarction, not acute ischemic stroke.[3] In an attempt to prevent medication errors, the FDA recommends healthcare professionals to use either brand name, Activase, or the generic name, alteplase.[13] To reduce risk of serious complications, all clinicians must recognize this potential error.

Alteplase dose is dependent on indication (AIS, acute MI, or acute massive pulmonary embolism). For AIS, the dose is 0.9 mg/kg (not to exceed 90 mg total dose) infused intravenously over 60 minutes with 10% of the total dose administered as an initial bolus over one minute. Pharmacists must reconstitute alteplase with sterile water for injection using aseptic technique, then inspect parenteral drug product for particulate matter and discoloration. The reconstituted vial should stand undisturbed for several minutes to allow any large bubbles to dissipate. Pharmacists must also consider route of administration. Most patients receive and respond to intravenous alteplase. Intra-arterial (tPA administered directly into the blood clot to help dissolve it) is an option for select patients nonresponsive to IV therapy.[18]

PAUSE AND PONDER: What drugs are indicated or contraindicated in the days and weeks after a person experiences a stroke?

During and after IV reperfusion therapy, pharmacists must monitor patients closely. Hemorrhage can occur one or more days after alteplase administration. Anticoagulants and antiplatelet drugs prior to, during, or after alteplase therapy increase risk of bleeding. Avoid anticoagulant and antiplatelet agents within the first 24 hours.[3] Monitor patients treated with alteplase during and for several hours after infusion for orolingual angioedema. Post market surveillance reveals many patients who develop angioedema received concomitant angiotensin-converting enzyme inhibitors. If angioedema develops, discontinue the alteplase infusion and promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids, epinephrine).

Blood pressure must be closely monitored throughout acute stroke management (see **Table 2**).

Prioritize Targeted Personalized Prevention

Stroke risk factors and contributors are multifaceted and complex. Systematic identification of risk factors and a targeted risk mitigation approach can help prevent stroke in high-risk patients and improve stroke sufferers’ prognosis.[24] Evidence shows pharmacist intervention in ischemic stroke outpatients improves stroke modifiable risk including blood pressure, low density lipoprotein, hemoglobin A1c, and smoking status.[16] Collectively, risk factor burden, inflammation, infection, socioeconomic status (SES), environmental exposures (climate), and lifestyle behaviors all contribute to stroke risk. Pharmacists have the opportunity to alter at-risk patients’ trajectory by appropriate risk mitigation education, use of available tools, and implementation of services. Furthermore, stroke is the leading preventable cause of disability.[1]

Blood pressure control is the most important preventive measure for stroke. Uncontrolled hypertension is the most common

Table 2. Hypertension Management in AIS Candidates for Emergency Reperfusion Therapy[12]

Prior to IV fibrinolytic therapy: BP goal: <185/110	During IV fibrinolytic: BP goal: ≤180/105	First 24 hours after treatment: BP goal: 180/105
BP >185/110 mm Hg: carefully lower before IV fibrinolytic therapy initiation. Labetalol 10-29 mg IV over 1-2 minutes, may repeat once Nicardipine 5mg/h IV, titrate up by 2.5 mg/hour every 5-15 minutes (max 15 mg/hour) Clevidipine 1-2 mg/h IV, titrate by doubling dose every 2-5 minutes (max 21 mg/hour) Other agents: hydralazine, enalaprilat	For 2 hours after infusion start: monitor every 15 minutes Hour 2 after infusion start-hour 8: monitor every 30 minutes For 16 hours more: monitor every hour	Rigorous BP control for 24 hours (keep BP <180/105 mm Hg during and after infusion).

cause of hemorrhagic stroke; it instigates a weakened blood vessel, like an aneurysm or arteriovenous malformation, and the vessel bursts.[13] Clinicians categorize hemorrhagic strokes by the location of the hemorrhage (i.e., intracerebral or subarachnoid). Approximately 87% of hemorrhagic strokes are due to intracerebral hemorrhage and as many as 80% of primary intracranial hemorrhages occur after chronic hypertension compromises small vessels.[13] Other causes of ICH include anticoagulant and antiplatelet use, drug use, and congenital vascular abnormalities.[13] Additionally, the risk for a first AIS is directly related to blood pressure starting with a systolic blood pressure (SBP) as low as 115 mmHg.[25] Meta-analysis performed among stroke-free individuals estimate BP lowering is associated with 30% to 40% stroke risk reduction.[25]

Current evidence clearly confirms anti-hypertensive medication reduces the risk of recurrent stroke and further supporting evidence continues to accrue.[25] Larger reductions in SBP tend to be associated with greater risk reduction of recurrent stroke.[25] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) found active hypertension therapy reduced fatal and nonfatal stroke by 28% among patients with history of stroke or TIA.[25] PROGRESSS participants were randomized to an angiotensin-converting enzyme inhibitor (perindopril) with or without a diuretic (indapamide). Most evidence supports diuretics or combination of angiotensin-converting enzyme inhibitor and diuretic to reduce blood pressure and stroke risk.[25] Some patients may require early acute phase intensification of antihypertensive therapy, whereas others may have a temporary hypertensive response; it's important to adjust therapy accordingly. Guidelines recommend antihypertensive therapy reintroduction or initiation immediately after TIA, a delay of 24 to 72 hours after AIS in most patients, and a longer waiting period if neurologically unstable.[25] Antihypertensive agent selection, BP goals, and time to initiated therapy should be individualized and determined on a case-by-case basis.[25]

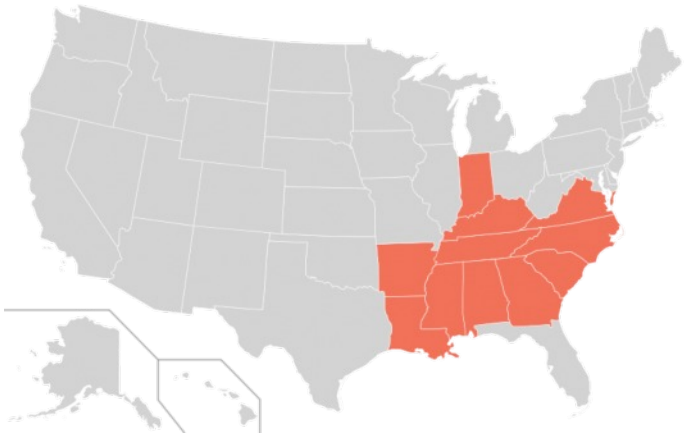
Tech Talk: Promote Heart-Healthy Lifestyles

- All patients can benefit from living "heart healthy" lives. Educated healthcare professionals can take a systematic approach to bridge the gap between patient healthcare goals and reality through education. Pharmacy technicians practice at the frontlines with patients and can make impactful behavioral recommendations to reduce stroke risk.

- Some behavioral interventions include: diet rich in fruits, vegetables, low-fat dairy products, Mediterranean diet, reduce salt intake, increase physical activity (regular aerobic physical activity), limit alcohol consumption, smoking cessation, address social determinants of health.[25,26]

Stroke Risk Factor Disparity

Diverging trends in stroke incidence and mortality rates in high-income compared to low- and middle-income countries necessitate further study.[4] Global incidence and outcome studies are challenging due to lack of comparable data, between-country geographical differences, and large ethnic/racial disparities.[4] The WHO clinical time-dependent definition of stroke and TIA allows population-based stroke incidence studies with maximally complete case ascertainment of fatal and nonfatal, and hospitalized and non-hospitalized events.[4] Current criteria for population-based stroke incidence studies incorporates the standard WHO definition for study comparability over time and between locations.[4] Epidemiologic studies that use the AHA/ASA tissue-based stroke definition, based on neuropathological, neuroimaging, and clinical evidence, limit data. Those studies will include only hospitals with appropriate neuroimaging and reporting technology, and trained providers.[4] Accurate and comparable population-based stroke incidence and outcome data provide the basis for evidence-based stroke care, resource allocation, and ingenuity.[4]



The Stroke Belt region of the United States.

Global geographic disparity in stroke mortality are further complicated by regional variabilities. More than 40 years of data reveal significantly higher stroke mortality in the Southeastern United States compared to the national average.[27] The National Heart Lung and Blood Institute defines **The Stroke Belt** as states with age-adjusted stroke mortality at least 10% above the national rate. Death rates among 35 to 54-year-olds who live in North Carolina, South Carolina, and Georgia are double the national rate.[9,27] Hypertension, diabetes mellitus, obesity, and behavioral factors like substance abuse (i.e., opioids, tobacco, alcohol) contribute to early onset stroke risk.[24] Although national declines in stroke mortality rates over the decade reduced the absolute magnitude of Stroke Belt disparity, the geographic disparity persists. Stroke deaths in the Southeastern Census Region continue to increase, as the rest of the nation plateaus.[24,27] To combat the climbing mortality in the Stroke Belt, we must understand the factors contributing to the geographic disparity. Two main forces can drive a geographic region to a higher mortality rate:

A. Higher incidence (more stroke cases in the region) or
B. Higher case fatality (stroke patients from the region are more likely to die)

Research suggests that both higher incidence of stroke and higher case fatality rates are seen in the Southeast, but the risk from higher incidence predominates.[27] Explanations for the higher stroke mortality in this region remain speculative. Some potential contributors are higher risk factor burden, higher levels of inflammation and infection, lower SES, and smaller contributions from environmental exposures and lifestyle choices. A large portion of Stroke Belt residents live in rural areas, which have been associated with higher mortality compared with urban areas.[27] Data from the REGARDS analysis suggest an increasing stroke incidence in areas of higher stroke mortality but a less consistent pattern for increasing case-fatality in these areas. Researchers suggest community-based efforts to reduce disparities in high stroke mortality areas. The REGARDS analysis assessed the association between SES (using six neighborhood socioeconomic variables assessed for the census block of the participant) and found a strong association of lower neighborhood SES with stroke risk (HR=1.60 [95% CI, 1.33-1.93]).[27]

High Risk of Stroke Recurrence Requires Secondary Prevention

Stroke is a catastrophic event for survivors and their loved ones. Among stroke survivors, approximately 31% require assistance with activities of daily living, 20% require assistance with ambulation, and 16% require institutional care.[9] A National Stroke Association survey of 523 long-term stroke survivors reported 87% had ongoing motor problems, 54% had trouble walking, 52% had trouble with hand movements, and 58% experienced spasticity.[28,29] The neurologic deficit caused by stroke varies depending upon the location of tissue damage, so the rehabilitation process looks different for each post-stroke patient. Similar to TIAs, silent infarcts may leave no immediate impairment, but both events increase risk for future ischemic stroke and call for prevention measures.[25]

Within the first hours and days after an AIS, the risk of recurrent events is high and the cumulative rate of recurrent stroke reaches 15% at 10 years.[24,26] Patient-specific characteristics including age, event type, comorbidities, and adherence to preventive therapies contribute to individual future risk.[25] These factors justify an early, aggressive preventive approach and optimization of longitudinal management thereafter.[26]

MEDICATION IN SECONDARY PREVENTION

Medication is the cornerstone for stroke treatment and prevention, so pharmacist intervention is critical. Mainstay therapies for secondary stroke prevention include antihypertensive, antiplatelet or anticoagulant, cholesterol-lowering, and glycemic control therapies.[25,26]

Antiplatelets and Anticoagulants

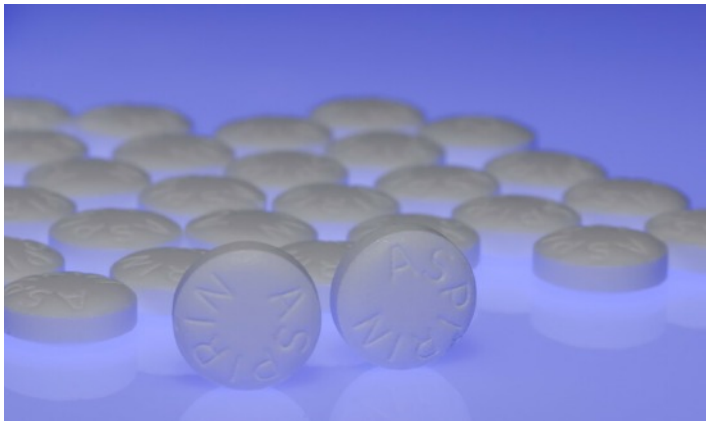
Antiplatelet therapy with aspirin is the default antithrombotic approach for most stroke subtypes' secondary prevention. But, not all patients are candidates for secondary stroke prevention with antiplatelet or anticoagulant therapy. Providers should consider individualized regimens for each patient carefully. Guidelines do not recommend triple antiplatelet therapy (aspirin, clopidogrel, dipyridamole) for secondary stroke prevention. Cilostazol and ticagrelor remain investigational antiplatelet agents with an unclear role.

Aspirin

Aspirin inhibits platelet aggregation by irreversibly blocking thromboxane A2 formation.[12,25,26] The 2019 AHA/ASA guidelines recommend administration of aspirin (cited trials investigated doses of 160 to 325 mg) within 24 to 48 hours after stroke onset in most AIS patients.[12] If dysphagia or aspiration are concerns, rectal or nasogastric administration of aspirin is appropriate. During the early subacute period after stroke (first 12 weeks) when the risk of recurrent stroke is high, aspirin therapy may be particularly beneficial.[26] Most post-AIS patient should continue low dose (81 mg/day) aspirin therapy long term.[26]

Dual Antiplatelet Therapy (DAPT)

Clopidogrel, a thienopyridine prodrug activated by CYP2C19 isoenzyme, inhibits adenosine diphosphate receptors involved in platelet activation and aggregation. CHANCE (Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events) studied Chinese patients presenting within 24 hours of symptom onset with either minor stroke (NIHSS score of 3 or below) or high-risk TIA ($ABCD^2$ score [age, blood pressure, clinical features, duration, diabetes mellitus] of at least 4). Patients were randomized to aspirin and clopidogrel for the first 21 days, then just clopidogrel until day 90, or aspirin and placebo for 90 days. POINT (the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial) had a similar study design, and both studies found a benefit with short-term dual antiplatelet therapy. Reported bleeding risks were higher in POINT, likely because clopidogrel loading dose was 600 mg compared to 300 mg in CHANCE. Interestingly, a CHANCE genetic substudy found that DAPT has limited benefit in carriers of CYP2C19 loss-of-function alleles.[26] So, after a minor noncardioembolic ischemic stroke or high-risk TIA not treated with IV alteplase, starting DAPT within 24 hours after symptom onset and continuing it for 21 days reduces recurrent AIS risk for up to 90 days.[12]



Warfarin and Direct Oral Anticoagulants

Cardioembolic strokes including but not limited to nonvalvular atrial fibrillation and left atrial or left ventricular thrombus, require secondary prevention with anticoagulation. Atrial fibrillation (Afib) patients are five times more likely to experience a stroke. Direct oral anticoagulants (DOACs) help reduce that risk, but one of the most dreaded complications of DOACs is ICH.[11] For more information on appropriate DOAC use, view UConn's You Asked for it "DOAC-Associated Bleeding: Risks and Reversal Strategies" Continuing Education.

Warfarin, a vitamin K antagonist, inhibits activity of cloting Factors II (prothrombin), VII, IX, and X. Warfarin therapy can challenge patients and providers. Patients must monitor dietary vitamin K intake and adhere to regular laboratory monitoring. Providers must consider the delayed onset of anticoagulation, significant drug-drug interactions, and doses based on international normalized ratio (INR) value. High INR increases bleeding risks, and low INR risks thromboembolism. Despite warfarin's pitfalls for secondary prevention measures, it prevents primary stroke in patients with nonvalvular atrial fibrillation effectively.[26]

DOACs appear to have similar efficacy for preventing thromboembolic events and a lower intracranial hemorrhage risk than warfarin. Dabigatran is a direct thrombin inhibitor, whereas rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors. The DOACs have a number of advantages over warfarin including fixed dosing, fewer drug interactions, and rapid predictable onset of action. The COMPASS trial randomized patients with stable atherosclerotic vascular disease to rivaroxaban 2.5 mg plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg daily. After 23 months, the trial was stopped early after rivaroxaban 2.5 mg plus aspirin demonstrated superiority in cardiovascular death, stroke, or myocardial infarction prevention. However the study excluded patients with a history of stroke within one month, previous intracerebral hemorrhage, or history of lacunar stroke.[26] So, providers require further studies on the role for low dose DOAC in combination with aspirin for secondary stroke prevention.

Table 3. Patient and Caregiver Education[16]	
Organization	**Program**
American Heart Association (800) AHA-USA-1 (242-8721) https://www.heart.org/	**HeartCare™ Channel** ● Providers can assign, deliver, and track patient education through the EMR ● Patient 24/7 access to post-discharge videos and printable resources
American Stroke Association (a division of the AHA) (800) AHA-USA-1 (242-8721) https://www.stroke.org/	**Stroke Hero Toolkit** ● Adults can empower youth to become stroke heroes ● Educators, mentors, and advocates, can become Stroke Hero Trainers
Centers for Disease Control and Prevention https://www.cdc.gov/stroke	**Stroke and You Series** ● Printable stroke education handouts for patients that highlight prevention
Internet Stroke Center (214) 648-311 http://www.strokecenter.org/	**Stroke Information** ● Website for caregivers and patients to learn more about stroke

Cholesterol Lowering Therapy

Some epidemiologic data reveals a modest link between high serum low-density lipoprotein cholesterol (LDL-C) and risk of ischemic stroke. Reduction of LDL-C serum lipid biomarker with 3-hydroxy-3-methylglutaryl coenzyme A reductase [HMG-CoA] inhibitors (statins) reduces stroke risk in select patients. SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) randomized 4731 post-stroke or TIA patients with no known history of coronary heart disease and LDL-C levels 100-190 mg/dL to atorvastatin 80 mg daily or placebo. The five year absolute reduction in cardiovascular event risk was 3.5% in the high-dose statin group (HR, 0.8; 95% CI, 0.69-0.92; P=0.002). However, some evidence suggests an association of low LDL-C and heightened ICH risk.[25]

BRAIN REHABILITATION AND RECOVERY

Beyond counseling patients on secondary prevention measures, pharmacists can ensure medication access and affordability, and build relationships to support long-lasting patient health and wellness. Healthcare providers must raise awareness of the many resources and tools available to post-stroke patients and caregivers. The Investigation of Stroke Needs (INVISON) Study, a qualitative longitudinal cohort study of patients with ICH, revealed that despite formal stroke education during hospitalization, patients report[30]

1. Lack of stroke knowledge/awareness
2. Need for stroke education
3. Fear of recurrent stroke and comorbid diseases

Also in this study, the majority of ICH survivors also had no memory of their hospitalizations.[30] Since patient's forget up to 80% of medical information healthcare practitioners provide immediately, pharmacists must work as effective liaisons between practitioners and patients.[14] Ley's model on effective communication in medical practice emphasizes the importance of patient understanding and satisfaction with treatment.[3] Mode of communication is also highly relevant. Most medical advice is spoken, however most people remember written information better.[14] Consider each patient's health literacy along with technology skills when providing materials. Some patients may prefer a written guide; others may prefer web-based access to information. **Table 3** lists reputable, patient-friendly resources.

CONCLUSION

Communication and collaboration between all healthcare team players is crucial to make a lasting impact on global stroke burden. Pharmacists play an integral role as liaisons between the patient and healthcare team to raise awareness of stroke urgency and stroke care and to implement services to improve access to care. Set attainable and measurable goals in your practice setting, involve others, and take action together. Goals can mirror national initiatives like the Healthy People 2020 objectives, engage a system-wide enterprise to promote access to stroke certified centers, or enrich modern evidence-based practices. Care providers with committed mindsets can work together to implement patient-centered personalized treatment and prevention approaches, optimize medication use, use shared decision-making, and ultimately reduce global stroke burden.[31]

Figure 1 (next page) provides suggestions to maximize your role in stroke treatment and prevention.

Figure 1. Maximizing the Pharmacy Team's Role in Stroke Prevention and Treatment

Best

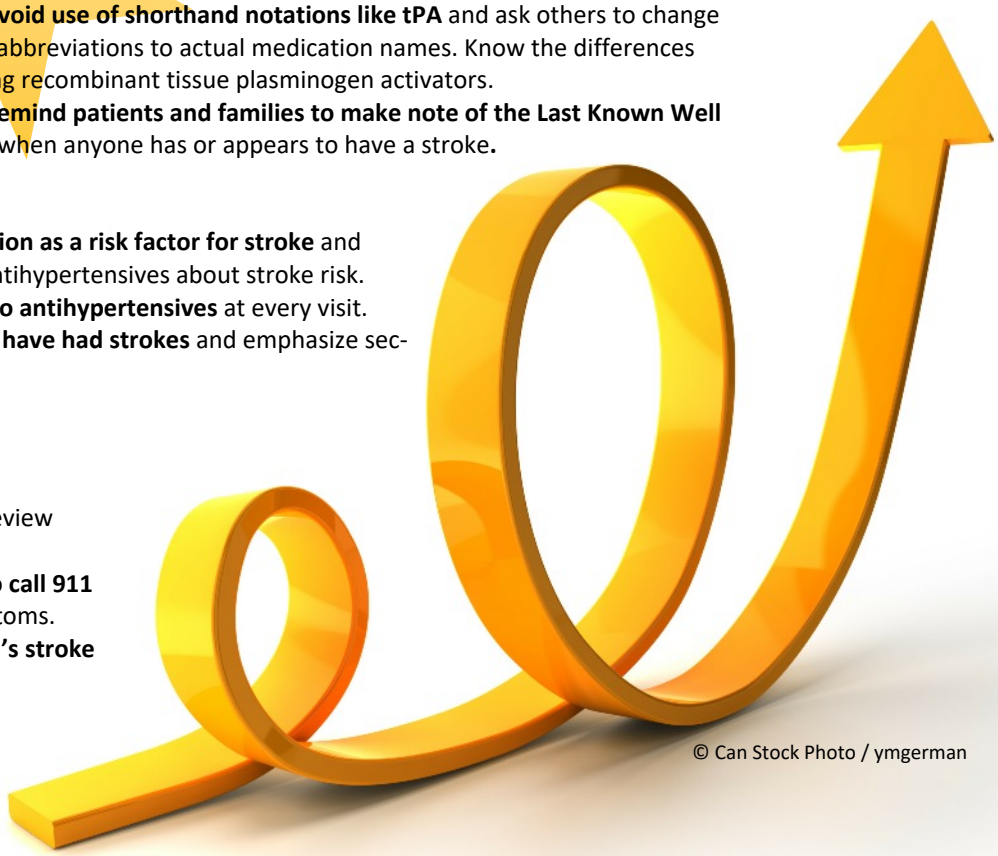
1. **Be COMMUNITY CHAMPIONS.** Actively **heighten awareness of stroke** and its complications and download and use the Stroke Hero Toolkit.
2. **Avoid use of shorthand notations like tPA** and ask others to change risky abbreviations to actual medication names. Know the differences among recombinant tissue plasminogen activators.
3. **Remind patients and families to make note of the Last Known Well time** when anyone has or appears to have a stroke.

Better

1. **Recognize hypertension as a risk factor for stroke** and counsel all patients on antihypertensives about stroke risk.
2. **Monitor adherence to antihypertensives** at every visit.
3. **Talk to patients who have had strokes** and emphasize secondary prevention.

Good

1. **Know stroke's symptoms,** and review them periodically.
2. **Never hesitate to tell patients to call 911** if they are experiencing stroke symptoms.
3. **Determine your geographic area's stroke profile.**



REFERENCES

1. American Heart Association. Heart disease and stroke statistics 2019. Available at https://professional.heart.org/idc/groups/ahamahpublic/@wcm/@sop/@smd/documents/downloadable/ucm_503396.pdf. Accessed January 7, 2020.
2. Engelhardt E. Apoplexy, cerebrovascular disease, and stroke: historical evolution of terms and definitions. *Dement Neuropsychol.* 2017;11(4):449-453.
3. Michaels AD, Spinler SA, Leeper B, et al; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, Council on Quality of Care and Outcomes Research; Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation; Council on Cardiovascular Nursing; Stroke Council. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. *Circulation*. 2010;121(14):1664-1682.
4. Feigin V, Norrving B, Sudlow C, Sacco RL. Updated criteria for population-based stroke and transient ischemic attack incidence studies for the 21st Century. *Stroke.* 2018;49:2248-2255.
5. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st Century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. 2013;44(7):2064-2089.
6. Stroke Alliance For Europe. New ICD 11 stroke classification will support global efforts to improve prevention, treatment, and outcomes. Available at https://www.safestroke.eu/2018/06/29/new-icd-11-stroke-classification-will-support-global-efforts-to-improve-prevention-treatment-and-outcomes/. Accessed May 29, 2020.
7. Fang J, Keenan NL, Ayala C, et al. Awareness of stroke warning symptoms—13 states and the District of Columbia, 2005. *MMWR* 2008;57:481-485.
8. U.S. Centers for Disease Control and Prevention. Preventing Stroke Deaths. Available at https://www.cdc.gov/vitalsigns/stroke/index.html. Accessed May 17, 2020.
9. CAST: Carolina Acute Stroke Training. Available at http://learn.pharmacy.unc.edu/strokecare/node/300. Accessed May 3, 2020.
10. World Health Organization. About 9 Voluntary Global Targets. https://www.who.int/nmh/ncd-tools/definition-targets/en/. Accessed May 29, 2020.
11. Bernhardt J, Zorowitz RD, Becker KJ, et al. Advances in stroke in 2017. *Stroke.* 2018;49(5)174-199.
12. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke. 2019;50(12):344-418.
13. Wisconsin Coverdell Stroke Program. Best practices to improve coordinated care for emergency medical service professionals. Available at https://www.dhs.wisconsin.gov/publications/p01158.pdf. Accessed June 23, 2020.
14. Kessels RP. Patients' memory for medical information. *J R Soc Med.* 2003;96(5):219-222.
15. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
16. NetCE. 90283: Ischemic stroke. Available at https://www.netce.com/coursecontent.php?courseid=1977. Accessed May 2, 2020.
17. Peña ID, Borlongan C, Shen G, Davis W. Strategies to extend thrombolytic time window for ischemic stroke treatment: an unmet clinical need. *Stroke*. 2017;19(1):50-60.
18. Joint Commission. Specifications Manual for Joint Commission National Quality Measures. https://manual.jointcommission.org/releases/TJC2020A1/MIF0292.html. Accessed June 14, 2020.
19. Tissue plasminogen activator for acute ischemic stroke: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581-1587.
20. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329.
21. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695-1703.
22. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309:2480-2488.
23. Health Grades Inc. Patient safety in American hospitals. Golden, Colo: Health Grades Inc; 2004.
24. Putaala J. Ischemic Stroke in Young Adults. *Continuum (Minneap Minn)*. 2020;26(2):386-414.
25. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke.* 2014;2160-2236.
26. Kim AS. Medical management for secondary stroke prevention. *Continuum (Minneap Minn).* 2020;26(2):435-456.
27. Howard G, Howard V. Twenty years of progress toward understanding the Stroke Belt. *Stroke*. 2020;51(3):742-750.
28. Ostwald SK, Davis S, Hersch G, et al. Evidence-based educational guidelines for stroke survivors after discharge home. *J Neurosci Nurs.* 2008;40(3):173-191.
29. Jones VN. The forgotten survivor. *Stroke Smart*. 2006. Available at www.stroke.org/site/PageServer?pagename=SS_MAG_so2006_feature_forgot. Accessed May 13, 2020.
30. Ing MM, Linton KF, Vento MA, et al. Investigation of Stroke Needs (INVISON) Study: Stroke Awareness and Education. *Hawaii J Med Public Health.* 2015;74(4):141-145.
31. ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *J Am Coll Cardiol.* 2019;74(3)177-232.