REVIEW ARTICLE

Update on Stroke Management

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Stroke affects nearly 800,000 people in the United States, and is a leading cause of disability and mortality. Increasing age is one of the most significant risk factors for stroke, and as our population continues to age, stroke is expected to become more prevalent. Strokes are categorized by either an ischemic event that impedes oxygen delivery to brain tissue, or by an intracranial hemorrhage. They present with similar symptoms, but must be correctly differentiated, as they are treated differently. Early diagnosis and treatment are key to successful patient prognosis. With an ischemic stroke, thrombolytics can reperfuse the affected tissue while it still remains viable. Likewise, early blood pressure management in a hemorrhagic stroke may decrease hematoma expansion and improve quality of life. Early management, along with secondary prevention of recurrent stroke and early physical therapy can safely lead to decreased neurological deficit and better functionality for patients.

INTRODUCTION

Stroke, or cerebrovascular accident, affects approximately 795,000 people in the United States each year and is a leading cause of adult disability.[1] According to the American Heart Association, stroke accounted for one of every 19 deaths in 2009.[1] The incidence of stroke in persons between the ages of 60 and 79 is 6.9% for women and 6.2% for men and increases to 13.8% and 13.9%, respectively, in persons over 80 years old.[1] As our population continues to age, epidemiologic studies indicate that the incidence of stroke will also rise.[2]

Most strokes are caused by an ischemic event, such as thrombosis, which interferes with the blood flow to the brain; common causes of ischemic stroke are listed in Table 1. Approximately 15% of strokes are due to an intracranial bleed, primarily due to cerebral aneurysms and intracerebral AV malformations.[1] In either case, there is narrow window in which the brain tissue remains salvageable, thus acting swiftly to diagnose, evaluate and treat the patient is essential.[3] After treatment of the acute event, modifiable risk factors for stroke such as hypertension and hyperlipidemia should be targeted in order to reduce the risk for subsequent events. Large tertiary care or university-based institutions may have "stroke teams" to provide specialized care for patients with cerebrovascular accidents. This review article provides the latest updates and standards of care in the management of both ischemic and hemorrhagic stroke for the primary care physician providing care to patients in emergency departments of small or rural hospitals.

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TABLE 1: Causes of ischemic stroke

Thrombosis	Lacunar strokes
	Large vessel thrombosis
	Dehydration
Cardioembolism	Atrial fibrillation
	Mural thrombus
	Dilated cardiomyopathy
	Ventricular aneurysm
	Endocarditis
	Patent foramen ovale
	Atrial septal defect
	Atrial myxoma
Hypercoagulable states	Protein S/C deficiencies
	Antithrombin III deficiency
	Factor V Leiden
	Antiphospholipid Syndrome
	Sickle Cell anemia
	Systemic malignancy
	Polycythemia Vera
	Thrombocytosis
	Thrombotic thrombocytopenic purpura
	Nephrotic syndrome
	Oral contraceptives
Vasculitis	Polyarteritis nodosum
	Takayasu's arteritis
	Giant cell arteritis
	Wegener's
	Systemic lupus erythematosus
Drugs	Cocaine
	Amphetamines

TABLE 2: National Institute of Health Stroke Scale (NIHSS)

Item	Scale
Level of consciousness - Alertness	0-Alert 1-Not Alert, but can be aroused 2-Not Alert, takes repeated effort 3-Unresponsive, or only reflex motor effects
Orientation questions: What is the month and his/her age	0-Answers both correctly 1-Answers one correctly 2-Answers neither correctly
Response to commands: Open and close eyes, grip and release	0-Performs both tasks correctly 1-Performs one task correctly 2-Performs neither task correctly
Best gaze - horizontal eye movement	0-Normal 1-Partial gaze palsy 2-Forced deviation or total gaze paresis
Visual field	0-No visual loss 1-Partial hemianopia 2-Complete hemianopia 3-Bilateral hemianopia; cortical blindness
Facial palsy	0-Normal 1-Minor Paralysis 2-Partial Paralysis 3-Complete Paralysis
Motor arm	0-No drift 1-Drift 2-Some effort against gravity 3-No effort against gravity 4-No movement
Motor leg	0-No drift 1-Drift 2-Some effort against gravity 3-No effort against gravity 4-No movement
Limb ataxia	0-Absent 1-Present in one limb 2-Present in two limbs
Sensory	0-Normal 1-Mild-to-moderate sensory deficit 2-Severe sensory deficit
Best language	0-No aphasia 1-Mild-to-moderate aphasia 2-Severe aphasia 3-Mute, global aphasia
Dysarthria - clarity of articulation	0-Normal 1-Mild-to-moderate dysarthria 2-Severe dysarthria
Extinction and inattention	0-No abnormality 1-Visual, tactile, auditory, spatial, or personal inattention 2-Profound hemi-inattention to more than one modality

Adapted from: National Institute of Health, National Institute of Neurological Disorders and Stroke (NINDS). National Institute of Health Stroke Scale.

Available at http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf.

IMMEDIATE ASSESSMENT AND STABILIZATION

As with any emergency, when a patient presents with symptoms consistent with a stroke, the initial step is stabilization of the airway and support of breathing and circulation. Because hypoxemia may worsen the effects of cerebral ischemia, oxygen saturation should be above 95%.[4] Volume status should be addressed and dehydration corrected with normal saline. A neurologic examination should be performed using the National Institutes of Health Stroke Scale to determine the neurologic deficit (Table 2),[5] and all stroke-mimicking differentials should be excluded including hypoglycemia, seizure, intracranial tumor, migraine and metabolic encephalopathy.[6] A thorough history should be obtained if possible, in which the most important component is the time at which the patient was last known to be symptom free. A series of laboratory tests including blood glucose levels, complete blood count, electrolytes, prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT) and EKG should be obtained to aid in the differential and management of the patient.[7] Brain imaging with non-contrast computed tomography (CT) can quickly rule out intracranial hemorrhage; however, subarachnoid hemorrhage may be missed.[8] If the stroke patient presents with a sudden severe headache, an examination of the cerebrospinal fluid for blood is warranted.[7] Other limitations of CT include missing brainstem strokes and lack of information on the severity of the ischemic event. For these reasons, magnetic resonance imaging (MRI) is becoming a preferred method of imaging in early stroke treatment.[8] Once hemorrhagic stroke is ruled out, patients with an acute ischemic stroke may be assessed for potential thrombolytic therapy.

THROMBOLYTIC THERAPY

The goals of thrombolytic therapy in patients with ischemic stroke are to break down the clot occluding the affected artery and reperfuse the brain tissue. Time plays such a valuable role because the tissue must still be viable. Studies demonstrate that neurologic outcomes are best when thrombolytics are administered within 4.5 hours of symptom onset depending on patient risk categorization.[9] Eligibility criteria for treatment with thrombolytics and contraindications to their use are listed in Table 3. Recombinant tissue plasminogen activator (r-tPA) is currently the only FDA approved thrombolytic agent for the treatment of an acute ischemic stroke, as others have either failed or are still awaiting approval.[10] Recombinant tissue plasminogen activator causes thrombolysis by converting plasminogen into plasmin, a protease that degrades fibrin. Thrombolytic therapy has been proven to lead better neurological outcomes, with earlier discharges and lower NIHSS scores at time of discharge when used in the

management of ischemic stroke.[9] However, thrombolytics are not used in many cases, because 90 percent of patients fail to present within the narrow window of time in which therapy is both safe and effective.[10]

There is good evidence to support the use of r-tPA in eligible patients presenting within three hours of symptom onset. Functional outcomes are significantly improved; however, based on four studies with 930 patients there is no significant effect on overall mortality.[11,12] There is also an increased chance of favorable functional outcome when r-tPA is administered within the 3- to 4.5-hour window, although smaller than if given within three hours, 69 v. 154 excellent outcomes per 1,000, respectively.[11-13] Effects on mortality are neither beneficial nor detrimental. Treatment beyond 4.5 hours is associated with an increased risk of death with moderate effects on good functional outcomes.

There are potential risks to using thrombolytic therapy, which may render some patients ineligible. In fact, the potential serious risks, which include brain hemorrhage, prompted the National Institute of Health in 1980 to make the statement that thrombolytic therapy should be avoided altogether.[14] See Table 3 for the contraindications for thrombolytic therapy.

TABLE 3: Eligibility Requirements and Contraindications for Thrombolytic Therapy

Eligibility Requirements	Contraindications (0 - 3 hours)	Relative Contraindications (3- 4.5 hours)
1. Diagnosis of acute ischemic stroke with signs of neurological deficit 2. Onset of symptoms < 4.5 hours 3. Age 18 or older	1. Head trauma 2. Previous stroke within 3 months 3. Symptoms of subarachnoid hemorrhage 4. Previous intracranial hemorrhage 5. Elevated blood pressure (systolic > 185, diastolic > 110 mmHg) 6. Platelet count <100,000/mm^3 7. Heparin received within 48 hours 8. Blood glucose < 50mg/dL	1. Patient age > 80 years 2. NIHSS score > 25 (severe stroke) 3. Current use of oral anticoagulant 4. History of diabetes 5. Past ischemic stroke

Ref: Jauch EC, Saver JL, Adams Jr. HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870-947.

HEMORRHAGIC STROKE

Signs and symptoms of an intracranial bleed include a systolic pressure >220 mmHg, vomiting, severe headache, and/or coma. However, these symptoms are not specific for hemorrhagic stroke and thus non-contrast CT is the gold standard required for definitive diagnosis.[15] The morbidity and mortality associated with hemorrhagic stroke is extremely high, thus time to diagnosis is key to successful management.[15]

Patients at highest risk for hemorrhagic stroke are those on oral anticoagulants such as warfarin, those with coagulation deficiencies either congenital or acquired, and those with low platelet levels. The medical recommendation for patients on anticoagulant therapy presenting with intracranial bleeding is to normalize the INR using prothrombin complex concentrates, recombinant factor VIIa, and vitamin K as an adjunct.[16] Historically, fresh frozen plasma was used to reverse INR, but research suggests that prothrombin complex concentrates achieves a more rapid reversal.[17]

The blood pressure readings seen in individuals with hemorrhagic stroke are typically higher than in ischemic stroke. Hypertension in these patients could contribute to hematoma expansion, rebleeding, and overall more adverse outcomes.[18] Although the target blood pressure to provide the greatest benefit for hemorrhagic stroke patients is currently unknown, the Antihypertensive Therapy in Acute Cerebral Hemorrhage (ATACH) investigators demonstrated the feasibility and safety of acute blood pressure lowering within six hours of symptom onset, with a resulting decrease in hematoma expansion.[19] A recent study of nearly 3,000 patients with acute intracerebral hemorrhage indicated that while aggressive hypertension control (systolic blood pressure <140 mmHg) did not significantly reduce death, patients reported a significantly better overall health-related quality of life.[20] The majority of patients received intravenous urapidil, nicardipine, nimodipine, labetalol, nitroglycerin, or nitroprusside as blood pressure lowering treatment during the first 24 hours. Current guidelines do not specify the agent of choice in this patient population but endorse lowering systolic blood pressure to <140 mmHg.[15]

A concern in patients with intracranial hemorrhage is the potential for a rise in intracranial pressure from the mass effect of the hematoma and/or underlying hydrocephalus. The monitoring and treatment of increased intracranial pressure (ICP) remains controversial due to an absence of studies demonstrating its effectiveness. Current recommendations for monitoring and treatment of increased ICP are a Glasgow Coma Scale (GCS) score less than or equal to eight, evidence of herniation, intraventricular hemorrhage, or hydrocephalus.[15] Referral to a neurosurgeon is recommended for the management of these patients.

Surgical removal of intracranial hemorrhages remains controversial. The International Surgical Trial in Intracranial Hemorrhage (STICH) did not demonstrate that early surgery was beneficial in terms of mortality, function and low GCS when compared to conservative treatment.[21] Currently, surgery is only recommended as soon as possible for patients who show signs of brainstem compression or are neurologically declining, due to risk of compromising uninjured brain through a procedure that has yet to show great benefits.[15]

SECONDARY PREVENTION

Antiplatelets and Anticoagulants

One focus of research targets the risk versus benefit of antiplatelet therapy in acute ischemic stroke. Aspirin therapy could reduce recurrent ischemic events, but also could put the patient at risk for an intracranial bleed. The current recommendation by the American Heart Association suggests that aspirin therapy at an initial dose of 325mg should be administered 24-48 hours after an acute ischemic stroke in most patients.[7,22] Due to bleeding risk, aspirin is not recommended to be given within 24 hours of thrombolytic therapy.[7] The International Stroke Trial (IST), a randomized trial, demonstrated that patients allocated to aspirin therapy had significantly fewer recurrent events measured 14 days later compared to "avoid aspirin" group, with no significant increase in intracranial bleeds.[23]

Clopidogrel has also been researched as an antiplatelet alternative to aspirin therapy in prevention of acute ischemic stroke. The trial of clopidogrel versus aspirin in patients with recent myocardial infarction (MI), ischemic stroke or peripheral vascular disease (CAPRIE) demonstrated that in the long term clopidogrel is more effective in the reduction of ischemic stroke, MI or vascular death, 5.32% v. 5.83% respectively.[24] The combination of aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients offered no advantage over clopidogrel alone and substantially increased the risk of serious bleeding.[25]

Aspirin has also been compared to combination therapy with extended-release dipyridamole and aspirin for secondary prevention of stroke. A meta-analysis comparing the combination to aspirin alone concluded that aspirin plus dipyridamole was superior in preventing stroke and other vascular related events in patients suffering minor stroke or transient ischemic events without increasing the risk of bleeding.[26] Overall mortality between the two groups was not significantly different, however. Aspirin and extended-release dipyridamole has also been compared with clopidogrel to decrease recurrent stroke in a noninferiority trial.[27] Similar rates of recurrent stroke were observed with the two treatments. Research has also looked beyond the use of antiplatelet therapy in hopes to find a safer and more effective alternative. Cilostazol, a vasodilator with antiplatelet properties, has been compared with aspirin in patients with recent stroke, using a noninferiority study design. Cilostazol was shown to be noninferior to aspirin in preventing recurrent ischemic stroke; however, the rate of discontinuation with cilostazol was significantly higher due to adverse effects including headache, diarrhea, dizziness, palpitation and tachycardia.[28] Taking all the antiplatelet trials into account, the choice of therapy for the prevention of ischemic stroke should be made based on effectiveness, safety and tolerability of each agent.

The use of full-dose anticoagulation in the treatment of acute ischemic stroke to prevent recurrent events or improve neurologic outcomes is not recommended.[7] However, in patients with acute ischemic stroke and restricted mobility, early prophylaxis against venous thromboembolism with subcutaneous unfractionated or low molecular weight heparin is recommended.[29] Additionally, in patients with ischemic stroke and atrial fibrillation, therapeutic anticoagulation with warfarin or dabigatran is recommended to reduce recurrent stroke and mortality.[30,31] For patients with ischemic strokes, carotid doppler is a cost effective screening tool to evaluate extracranial stenosis that may benefit from surgical intervention to prevent subsequent strokes.[13] If embolic stroke is suspected, echocardiography is the imaging modality to look for potential cardiac sources of the emboli, such as mural thrombus, patent foramen ovale, ASD or valvular lesions. Transesophageal echocardiography (TEE) has been shown to be superior to transthoracic echocardiography in identifying a cardiac source of an embolic stroke.[32]

Blood Pressure Control

Hypertension is a known risk factor for the development of stroke. Additionally, both hypertension and hypotension in stroke patients are poor prognostic predictors. Increases in blood pressure puts the patient at risk for intracranial hemorrhage, but inadequate pressure interferes with sustaining the cerebral blood flow necessary to keep the brain perfused. Studies evaluating the effects of blood pressure lowering during acute ischemic stroke demonstrate inconsistent clinical outcomes. Therefore, the ideal blood pressure range in patients with acute stroke has yet to be determined. Current guidelines recommend not to lower blood pressure in the first 24 hours of acute ischemic stroke unless the blood pressure is > 220/120 mm Hg unless there are other medical conditions that would benefit from blood pressure lowering or thrombolytic therapy is being considered.[13] With regard to patients with intracerebral hemorrhage with systolic blood pressures of > 180 mm Hg and no evidence of elevated ICP, a target blood

pressure of 160/90 mm Hg is recommended.[15] As previously mentioned, however, blood pressure lowering to < 140 mm Hg is probably safe in patient with hemorrhagic stroke. In both cases, patients should be reexamined frequently during the acute period. Thereafter, blood pressure should be maintained within normal ranges.

Dyslipidemia

The prevalence of adult hypercholesterolemia in the United States is around 13.8%, with another 5.6% remaining undiagnosed.1 Dyslipidemia remains an important risk factor in the development of ischemic stroke. In fact, a comprehensive meta-analysis indicates that for every point increase in LDL cholesterol level, there is a 0.3% increased risk in mortality from stroke.[33] HMG Co-A reductase inhibitors reduce the risk of all cause death and nonhemorrhagic stroke and are indicated in patients for secondary prevention of a cardiovascular event.[33-35]

Blood Glucose Levels

Diabetes is a risk factor for a cerebral vascular accident. Sui et al. performed a prospective study that indicates that with fasting blood glucose levels starting at 110 mg/dL, for every 10 mg/dL increment increases there is 6% increase in the risk for a stroke event to occur.[36] Hyperglycemia in stroke patients is associated with a poorer prognosis, while hypoglycemia can cause stroke-mimicking symptoms and thus should be ruled out. A randomized trial of 72 stroke patients indicates that treatment of hyperglycemia with insulin was both safe and feasible.[37] However, a recent review of seven trials involving 1,296 participants demonstrated that maintaining glucose control between 72 and 135 mg/dl immediately after a stroke did not reduce death or dependence but increased symptomatic hypoglycemic events.[38]

Stroke Rehabilitation

The primary goals of post-stroke rehabilitation are to maximize patient functioning, limit neurological deficit, and to prevent complications, such as stroke reoccurence.[39] Starting rehabilitation early can provide patients with the best functional results.[40] Specialized stroke centers, or hospitals with stroke units, have standardized admission protocols that insure that consultations with speech, occupational and physical therapies get ordered in the first 24 hours of admission. Patients receiving therapy from a multidisciplinary team, which includes physicians, nurses, physical therapists, occupational therapists, speech therapists, family caregivers, and more, are associated with better clinical outcomes.[39] A small single-blind study in acute stroke patients demonstrated that early mobilization less than 24 hours after stroke is both safe, feasible and is associated with good functional outcomes at three and 12 months.[41] Thus,

TABLE 4: Key Recommendations for Practice

Clinical recommendations	Evidence rating	References
Patients presenting with an ischemic stroke that meet all eligibility criteria should receive treatment with tissue plasminogen activator within 3 hours of symptom onset.	A	Lees, Wardlaw
Patients presenting with an ischemic stroke within the 3 to 4.5-hour window that meet all eligibility criteria should receive treatment with tissue plasminogen activator.	A	Lees, Wardlaw
Aspirin therapy at an initial dose of 325mg should be administered 24 - 48 hours after an acute ischemic stroke in most patients but not within 24 hours of thrombolytic therapy.	A	Adams, Sandercock
In patients with hemorrhagic stroke, aggressive hypertension control (SBP < 140 mmHg) lowers the rate of hematoma expansion and improves quality of life.	A	Qureshi, Anderson
Initiate early physical and occupational therapy as soon as possible in patients suffering from either an ischemic or hemorrhagic stroke.	B	Cumming

A – Consistent, good quality patient oriented evidence.
B – Inconsistent or limited quality patient-oriented evidence.
C – Consensus, disease-oriented evidence, usual practice, expert opinion or case series.

Ref: Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature.
Am Fam Physician. 2004;69:548-56.

it is recommended to initiate early physical and occupational therapy as soon as possible in patients suffering from either an ischemic or hemorrhagic stroke.

SUMMARY

Stroke is the leading cause of disability in the United States.[1] The initial management of stroke should focus on immediate stabilization of the patient while differentiating whether the stroke is ischemic or hemorrhagic. Although certain symptoms can lead one toward a diagnosis of one over the other, brain images read by a neuroradiologist must confirm the diagnosis. Patients presenting with an ischemic stroke, that meet all eligibility criteria, should receive treatment with tissue plasminogen activator. Aspirin therapy should be started as soon as possible in ischemic stroke patients, but not within 24 hours of rtPA therapy. In hemorrhagic stroke, blood pressure management is important, as increases in blood pressure leads to expansion of the hematoma, increases in intracranial pressure, and thus worse outcomes. Finally, no matter what the diagnosis, early physical therapy and rehabilitation should take place to ensure patients regain as much functionality back as they can. Key recommendations for clinical practice are listed in Table 4 using Strength of Recommendation Taxonomy (SORT).[42]

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November/December 2013 Answers:
1. b 2. c 3. a 4. d 5. b 6. d 7. a 8. c 9. b 10. a

REFERENCES

1. American Heart Association Writing Group. Heart Disease and Stroke Statistics—2013 Update. A Report from the American Heart Association Circulation. 2013;127:e6-e245
2. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003;2:43-53.
3. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology. 2000;55:1649 –1655.
4. Kalafut MA, Saver JL. The acute stroke patient: the first six hours. In: Cohen SN, editor. Management of ischemic stroke. New York: McGraw-Hill; 2000. p. 17–52.
5. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology. 1999;53:126–131.
6. Smith W, English J, Claiborne S. Claiborne Johnston. Cerebrovascular Diseases. In: Fauci AS, Braunwald E, Kasper DL, et al. eds. Harrison's Principles of Internal Medicine, 17th edition, New York: McGraw Hill, 2008:2514.
7. Adams Jr. HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke : A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Stroke. 2007;38:1655-1711.
8. Jamieson DG. Diagnosis of ischemic stroke. Am J Med. 2009;122:S14-S20.
9. Rymer MM, Armstrong EP, Walker G, et al. Analysis of a coordinated stroke center and regional stroke network on access to acute therapy and clinical outcomes. Stroke. 2013;44:132-137.
10. Barreto AD. Intravenous thrombolytics for ischemic stroke. Neurotherapeutics. 2011;8:388-399.
11. Lees Kr, Bluhmki E, von Kummer R, et al. ECASS, ATLANTIS, NINDS and EPITHET rtPA Study Group. 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.
12. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischemic stroke. Cochrane Database Syst Rev. 2009;(4):CD000213.
13. Jauch EC, Saver JL, Adams Jr. HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870-947.
14. Sherry S, Bell WR, Duckhert FH, et al. Thrombolytic therapy in thrombosis: A National Institutes of Health Consensus Development Conference. Ann Intern Med. 1980;93:141-144.
15. Morgenstern LB, Hemphill III JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2010;41:2108-2129. Ansell J, Hirsh J, Hylek E. Pharmacology and management of the vitamin K antagonists:
16. American College of Chest Physicians Evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133(6Suppl):160S-198S.
17. Fredriksson K, Norrving B, Strömblad LB. Emergency reversal of anticoagulation after intracerebral hemorrhage. Stroke. 1992;23:972-977.

18. Jauch EC, Lindsell CJ, Adeoye O, et al. Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. Stroke. 2006;37:2061-2065.

19. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Investigators. Antihypertensive treatment of acute cerebral hemorrhage. Crit Care Med. 2010;38:637-648.

20. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage trial (INTERACT2) N Engl J Med. 2013. DOI:10.1056/NEJMoa1214609.

21. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365:387-397.

22. Sandercock PAG, Counsell C, Gubitz GJ, et al. Antiplatelet therapy for acute ischemic stroke [update of Cochrane Database Syst Rev. 2003;CD000029;PMID: 12804384]. Cochrane Database Syst Rev.2008;CD000029.

23. The International Stroke Trial (IST).A randomized trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997;349:1569–81.

24. CAPRIE Steering committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329-39.

25. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:331-7.

26. Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. Stroke. 2008;39:1358-1363.

27. Sacco RL, Diener H-C, Yusuf S, et al for the PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008; 359:1238-1251.

28. Shinohara Y, Katayama Y, Uchiyama S, et al. CSPS-2 group. Cilostazol for prevention of secondary stroke (CSPS-2): an aspirin-controlled, double-blind, randomized non-inferiority trial. Lancet Neurol. 2010;9:959-68.

29. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based practice guidelines. Chest. 2012;141(Suppl):e601S-36S.

30. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857-67.

31. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-based practice guidelines. Chest. 2012;141(Suppl):e531S-75S.

32. de Bruijn SFTM, Agema WRP, Lammers GJ, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. Stroke. 2006;37:2531-2534.

33. O'Regan C, Wu P, Arora P, et al. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am Journal of Medicine. 2008;121:24-33.

34. Collins R, Armitage J, Parish S, et al. for the Heart Protection Study Collaborative Study Group. Effects of cholesterol lowering with simvastatin on stroke and other major cardiovascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363:757-67.

35. Amarenco P, Bogousslavsky J, Callahan A III, et al. for the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549-59.

36. Sui X. A prospective study of fasting plasma glucose and risk of stroke in asymptomatic men. Mayo Clin Proc. 2011;86:1042-9.

37. Johnston KC, Hall CE, Kissela BM, et al. Glucose regulation in acute stroke patients (GRASP) trial: a randomized pilot trial. Stroke. 2009;40:3804-3809.

38. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst Rev. 2011;(9).

39. Duncan PW, Zorowitz R, Bates B, et al. Management of adult stroke rehabilitation care: a clinical practice guideline. Stroke. 2005;36(9):e100-43.

40. Knecht S, Hesse S, Oster, P. Rehabilitation after stroke. Dtsch Arztebl Int. 2011;108:600-6.

41. Cumming TB, Thrift AG, Collier JM, et al. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. Stroke. 2011;42:153-8.

42. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69:548-56.