CLINICAL CASE OF THE MONTH

A 49 Year-Old Man Who Presents with Left Sided Weakness: An Update on Ischemic Stroke

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CASE PRESENTATION

A 49 year-old man with a past medical history significant for essential hypertension, hyperlipidemia, and coronary artery disease status post percutaneous coronary intervention and stent placement in the right coronary artery in 2010 presented for evaluation of left hemiplegia. He was feeling well until three hours prior to presentation, at which time he fell while walking from his bedroom into the kitchen. After falling, he noticed that his left upper and lower extremities felt weak. He denied any symptoms preceding the fall or any loss of consciousness. On initial exam, the temperature was 99°F, the pulse was 93 beats per minute, the blood pressure was 191/100 mmHg, the respiratory rate was 22 breaths per minute, and the oxygen saturation was 100% while breathing room air. His neurological exam revealed diminished strength in the left upper extremity: 4/5 arm abduction and adduction of the left shoulder; 4/5 elbow and wrist extension and flexion; and 4/5 extension, abduction, and adduction of the digits. The patient also exhibited slight left upper extremity pronator drift. The strength was also diminished in the left lower extremity: 2/5 hip flexion, extension, and rotation; 3/5 knee flexion and extension; and 3/5 ankle dorsiflexion and plantar flexion. Initial NIH stroke scale score was 5, otherwise, there were no focal neurological deficits and the remainder of his exam was unremarkable. Initial computed tomography (CT) of the head was negative for any acute intracranial hemorrhage or infarct. A subsequent CT cerebral perfusion scan (Figure 1) was notable for areas of ischemia in the right cingulate gyrus as well as the medial frontal and parietal lobes. CT angiogram of the neck revealed bilateral atherosclerotic plaque in the carotid arteries; however, there was no evidence of any flow-limiting stenosis.

Given the patient's time of onset of symptoms, physical examination, and initial imaging findings, the decision was made to administer thrombolytics. After administration of tissue plasminogen activator (tPA), the patient was placed in the medical ICU for close observation. He experienced rapid improvement in his symptoms and within two hours his symptoms had completely resolved. MRI was later obtained which revealed small areas of infarct consistent with the distribution of ischemia initially revealed on the CT cerebral perfusion study (Figure 2). The patient was ultimately discharged with follow-up with his primary care provider and a neurologist on a regimen of aspirin, clopidogrel, hydrochlorothiazide, lisinopril, and high-intensity statin therapy. He was instructed to discontinue the aspirin after 21 days.

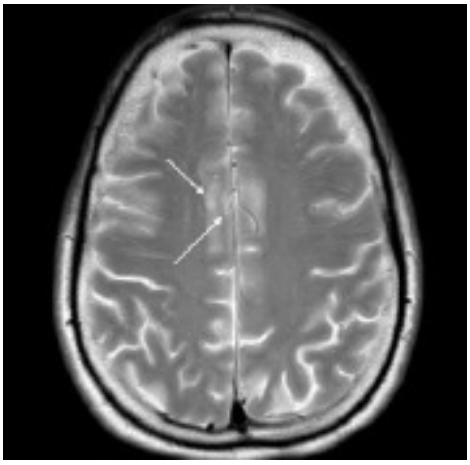

FIGURE 1: CT perfusion scan showing ischemic penumbra in the right cingulate gyrus (arrows pointing out affected area).

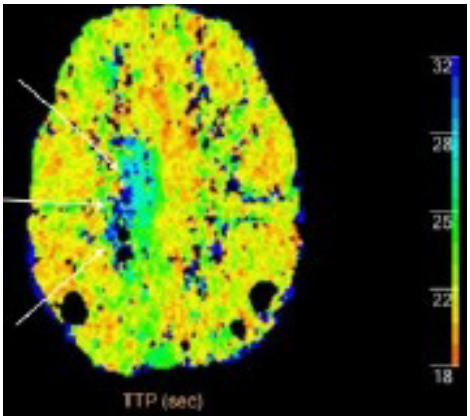

FIGURE 2: MRI T-2 weighted images showing punctuate areas of diffusion restriction in the right anterior cerebral artery territory (arrow pointing at affected areas.

EPIDEMIOLOGY

The incidence of all strokes in the U.S. is an estimated 795,000 people per year. Of these, nearly 25% occur in those with a history of prior stroke, i.e. about 185,000.[1] A minority of the total number of strokes will be hemorrhagic in nature, constituting approximately 13% of such events. The remaining 87% are comprised of ischemic strokes, which can be further broken down into lacunar strokes (25%), cardio-embolic strokes (25%), and large vessel strokes (50%).[2] Stroke is the fifth leading cause of death in the U.S., accounting for over 130,000 deaths annually.[3] In recent years, from 2001-2011, stroke mortality rates fell by a relative 35.1%, with the number of stroke deaths down 21.2%. This reduction in mortality is concomitant with increasing focus on the modifiable risk factors which can be changed, particularly hyperlipidemia, hypertension, diabetes mellitus, and tobacco use.[4] Of note, the mortality rate from stroke also varies with geographic region, with the southeastern U.S. having a disproportionately high amount of stroke deaths compared to other regions.[5] The overall cost of stroke and impact on the U.S. healthcare system is estimated to be approximately $34 billion dollars annually.[1]

PRIMARY PREVENTION

There are numerous non-modifiable and modifiable risk factors for ischemic stroke. Non-modifiable risk factors include age, sex, race, ethnicity, and low birth weight. The risk of ischemic stroke doubles for each successive decade after age 55.[6] Men have a higher incidence of stroke than women in all age groups with only two exceptions. The use of oral contraceptives in ages 35-44 years places women in this age group at higher risk for stroke than men.[7] The relative increase in earlier cardiac deaths of men age greater than 85 years old accounts for the other age group in which the female stroke mortality exceeds that of males.[8] African Americans and Hispanics have a higher incidence of stroke and increased stroke mortality compared with whites, a finding thought to be due to a higher prevalence of hypertension and diabetes in these populations.[9-15] A meta-analysis of cohort studies showed that a positive family history of stroke increases the risk of stroke by about 30%.[16] Despite adjustment for conventional stroke risk factors, a review of the Framingham study showed that children of parents with a history of stroke before age 65 years were three times more likely to have a stroke in their lifetime.[16] The possibility of a hereditary component to stroke risk remains a heavily studied concept.

Primary prevention of stroke includes alteration of modifiable risk factors, which vary widely and are generally similar to those risk factors for all other atherosclerotic vascular diseases (ASCVD), including hypertension, hyperlipidemia, atrial fibrillation, carotid stenosis, diabetes, nutrition, physical inactivity, obesity, smoking, and postmenopausal hormones.

Hypertension remains a major modifiable risk factor for ischemic stroke. Though it is clear that lowering blood pressure in all age groups and across all baseline blood pressures shows benefit in the prevention of stroke, the optimal blood pressure target and antihypertensive agent is less clear in primary prevention of stroke compared to secondary prevention. According to a 2003 meta-analysis of 23 randomized trials, there was a 32% relative risk reduction in patients on antihypertensive drug treatment versus placebo.[17] Innumerable trials and meta-analyses have been performed to compare specific antihypertensive agents. For example, diuretics where found to be superior to ACE inhibitors with in one meta-analysis,[17] while two independent studies found that calcium channel blockers were superior to ACE inhibitors.[18-19] The Blood Pressure Lowering Treatment Trialists' Collaboration was designed as a progressive systematic review of current data to evaluate up-to-date evidence on the effects of blood pressure on risk of atherosclerotic diseases. This comprehensive review concluded that in primary prevention of stroke, the degree of blood pressure lowering determined the magnitude of risk reduction.[20] In conclusion, while there is a definite benefit to lowering blood pressure as a means of primary prevention of stroke, to date no single class of antihypertensive agents has been shown to be superior in primary prevention.

Atrial fibrillation (AF) is another prevalent modifiable risk factor for stroke and singularly increases the mortality of stroke.[21] Atrial fibrillation, both sustained and paroxysmal, increases risk of embolic ischemic stroke by four to five fold and accounts for up to 10% of all ischemic strokes in the U.S.[22-24] Many scoring systems for assessing stroke risk in atrial fibrillation have emerged over time, but ultimately the first one to be validated by a randomized control trial was CHADS2 which allocated a single point for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus and two points for prior stroke or transient ischemic attack (TIA).[25-26] This scoring system was modified and verified by a randomized control trial in 2009 into CHA2DS2-VASc (Table 1), which separated the age category (assigning one point for age 65-74 years and two points for age ≥ 75 years), and added one point for the diagnosis of vascular disease (peripheral artery disease, MI, or aortic plaque) and one point for female sex.[27] This new scoring system was created to minimize the number of patients who were previously categorized as intermediate risk in favor of more definitive risk classification. It was thus determined that any patient with atrial fibrillation and a history of stoke or CHA2DS2-VASc ≥ two, where benefits outweigh the risk of anticoagulation, should be anticoagulated. In patients with very low-risk CHA2DS2-VASc of zero, it is reasonable to omit anticoagulation and consider aspirin therapy. Patients with a CHA2DS2-VASc of one have a clinical benefit that favors anticoagulation. However as per latest guidelines, it is up to physician discretion as to whether aspirin or anticoagulation is administered. Risk of stroke and benefit of anticoagulation should be balanced with risk of bleeding from anticoagulation. To assess this risk, the HAS-BLED scheme has emerged after verification by a randomized control trial for use in predicting major bleeding as a complication of anticoagulation.[28] One point each is assigned for hypertension, abnormal liver or renal function, past stroke, past history of or disposition for major bleeding, labile INR, age > 65 years, and use of certain drugs (ie: antiplatelet or nonsteroidal anti- inflammatory agent use) or alcohol abuse.[28] Scores greater than two are associated with significant increased risk of major bleeding and should undergo more rigorous monitoring of anticoagulation, especially in light of newer agents that generally require less frequent monitoring.

SCORE	CHADS2 ANNUAL STROKE RISK	CHA2DS2VASc2 ANNUAL STROKE RISK
0	1.90%	0%
1	2.80%	1.30%
2	4.00%	2.20%
3	5.90%	3.20%
4	8.50%	4%
5	12.50%	6.70%
6	18.20%	9.80%
7		9.60%
8		6.70%
9		15.20%

TABLE 1: CHA2DS2-VASc Scoring system

In recent years, with the emergence of novel oral anticoagulants (NOACs), physicians now have more choices when choosing anticoagulants. The FDA has approved five agents within three classes for the prevention of cardioembolic events in nonvalvular AF: Vitamin K antagonists (warfarin), direct thrombin inhibitors (dabigatran), and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). There are several landmark trials that have been performed to compare these agents in recent years.[29-32] These new agents have been shown to be safe and effective in primary prevention of strokes in patients with AF. However, no direct comparison of these novel agents is yet available. Physicians must weigh the strengths and weaknesses of these agents to choose the ideal agent for his or her patient.

Dyslipidemia is another well-documented risk factor for ischemic stroke. In general, treatment of hyperlipidemia with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., statins) have been shown to reduce risk of stroke by up to 21%.[33-34] Recently, a meta-analysis demonstrated that irrespective of age, sex, baseline LDL cholesterol or previous vascular disease, each 1 mmol/L reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1000 over five years.[33] This analysis in large part lead to the 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults that replaced the prior Adult Treatment Panel III for practitioners on management of hyperlipidemia in adults. These new guidelines transition focus away from specific lipid targets and rather incorporate a combination of variables including total cholesterol, HDL, sex, race, systolic BP, hypertension treatment, diabetes mellitus, and cigarette smoking, into a pooled cohort equation, which is then used to determine the 10-year risk of any ASCVD. This calculation then assists in separating patients who would benefit from statin therapy into four categories, with one major subset being those with an estimated 10-year ASCVD risk >7.5% requiring high intensity statin therapy.[34] All patients should be treated in accordance with the 2013 ACC/AHA guidelines for management of hyperlipidemia.

Several studies have shown benefit of carotid endarterectomy (CEA) in symptomatic (i.e., ipsilateral stroke or TIA) and asymptomatic patients with carotid stenosis. There are two major trials to date that compare the benefit of CEA versus medical management in primary prevention of stroke in patients noted to have carotid stenosis. The first trial was the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial which randomized exclusively asymptomatic patients with > 60% carotid stenosis to aspirin versus aspirin and CEA. The study was terminated prematurely at only 2.7 years owing to a clear benefit of surgical intervention over medical management [5 vs 11%; ARR 6%].[35] Subsequently the Asymptomatic Carotid Surgery Trial (ACST) increased the degree of carotid stenosis required to enroll in the trial to > 70% and verified similar benefit in favor of CEA versus medical management. (6.4 vs 11.8%).[36] These benefits were greater in men than women and not found to be statistically significant in patients age >75 years old.[36] As such, new guidelines now recommend prophylactic CEA in certain patients with high-grade (>70%) carotid stenosis based on carotid ultrasound if the surgical risk is less than 3% and estimated survival of over five years.[37-38] Internal carotid artery stenting (CAS) as an option for high-risk patients that would otherwise require surgery has emerged as a potential therapeutic option. The Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) trial included patients deemed high risk for CEA who had ≥ 80% carotid disease. Initial outcomes of stroke, MI, or death at 30 days favored CAS over CEA [5.4% vs 10.2%]; however, the long-term data at three years was disconcerting demonstrating up to 20% death rate in both groups which raises questions about the long term value of any intervention.[39] Subsequently, the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), which also included both symptomatic and asymptomatic patient with moderate to severe carotid stenosis (≥ 60% by conventional angiography or > 70–80% by noninvasive techniques), found no difference in rate of stroke, MI, or death (7.2 vs 6.8%) between CAS and CEA at four years.[40] Both trials where flawed in assessment of benefit in primary prevention as neither was powered to access asymptomatic patients alone nor did either include a medical management control group. The National Institute of Neurological Disorders and Stroke has sponsored an open label

randomized clinical trial, the Carotid Revascularization of Primary Prevention of Stroke (CREST-2) trial, to facilitate comparison of medical management versus CEA and CAS by way of a parallel two-armed clinical trial that is anticipated to be completed in 2020.

Diabetes is known to be an independent risk factor for macrovascular disease complications, including stroke. In fact, the risk of stroke have been shown to increase up to 3% per year of diabetes duration.[41] Diabeties as a risk factor for stroke should be aggressively treated, similar to other stroke risk factors such as hypertension and hyperlipidemia. However, tight glycemic control, while useful in prevention of microvascular complications, has not been shown to decrease stoke risk in a randomized trial.[42]

It must be emphasized that lifestyle modification, including but not limited to adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight, remains a critical component of the primary prevention of stroke. Diets low in sodium (USDA:<2300 mg/d; AHA < 1500 mg/d) and high in potassium (4700 mg/d)[43] as well as rich in fruits and vegetables, such as the Mediterranean[44] and DASH-style[45] diets, have been shown to reduce risk of stroke and are now recommended by AHA guidelines.[34] Both active and second-hand smoking increases risk of ischemic stroke and smoking cessation does seem to result in rapid reduction in the risk of atherosclerotic disease (stroke and other cardiovascular events) to a level that approaches, but does not reach, that of non-smokers.[46-47]

HOSPITAL MANAGEMENT

The initial assessment of a patient with suspected stroke should be expedited as treatment options are generally limited to the first six hours from symptom onset. Once the patient is stabilized, a history and physical exam should be obtained focusing on time of symptom onset, localization of the likely injury, and risk factors for stroke etiology. Stroke severity can be assessed using a validated scoring system such as the NIH Stroke Scale (NIHSS). Neuroimaging should be obtained within twenty minutes of patient arrival, and interpreted within forty-five minutes.[48] Noncontrast head CT is highly sensitive at ruling out intracerebral hemorrhage and also has the advantage of rapid turn- around time. Several advanced neuroimaging modalities are also available, including CT angiography, CT perfusion imaging, MR angiography, MR diffusion-weighted, and MR perfusion-weighted imaging, and are suitable alternatives in centers where these can be obtained without delay. An NIH stroke scale score (Table 2) should be calculated. This scoring system is based on certain physical exam parameters with scores ranging from 0-42.[48] It is generally accepted that severe strokes are classified as having an NIH stroke scale score of 15-20 or greater.

The most important next step, once intracerebral hemorrhage is ruled out, is whether to administer thrombolytics. All patients presenting within 4.5 hours of symptom onset should be considered for intravenous thrombolysis. In 2009, the AHA/ASA issued a focused update regarding expansion of the time window to 4.5 hours from symptom onset for treatment of acute stroke with IV tPA.[49] The administration of tPA for acute ischemic stroke was FDA approved in 1996 for select patients able to receive treatment within three hours of symptom onset. This was on the basis of the NINDS rtPA Stroke Trial which showed a favorable outcome for patients treated with tPA within 0-180 minutes of symptom onset, with a larger benefit for those receiving tPA in the initial 90 minute window [OR 2.11(95%CI 1.33-2.55) vs 1.69 (95% CI, 1.09-2.62)].[50] Extended time frames to initiate treatment were not studied in this trial. In 2008, results from the European Cooperative Acute Stroke Study (ECASS III) were published, which was designed to evaluate administration of tPA 3-4.5 hours after acute stroke symptom onset. Similar exclusion criteria were used as were previously recommended by the AHA/ASA, with the addition of certain criteria which may predispose to intracerebral hemorrhage, including age greater than eighty, NIHSS greater than 25, use of oral anticoagulants regardless of INR, greater than one-third MCA territory involvement on CT, and concomitant presence of diabetes mellitus and history of old ischemic event. Patients who received tPA had improved function at 90 days compared to placebo (mRS 0-1 53.4% vs 45.2%, OR 1.34) with no significant difference in mortality, although there was a higher incidence of intracerebral hemorrhage. A pooled analysis of four trials showed similar benefit in administration of tPA out to 4.5 hours from symptom onset.[51] However it is important to note that outcomes are consistently better with earlier administration of tPA, and delay in treatment should be strictly avoided.

Patients who receive tPA should be admitted to the intensive care unit for close monitoring of blood pressure and neurological exam. Blood pressure is strictly monitored during the initial twenty-four hour period following tPA administration, with checks performed every fifteen minutes for the first two hours, then every thirty minutes for six hours, and then every one hour for sixteen hours.[52] Blood pressure should be maintained below 180/105 to minimize risk of spontaneous intracerebral hemorrhage. If lowering is indicated, titratable infusions of labetalol or nicardipine are preferred in an effort to avoid lowering blood pressure more than 15% in the first twenty-four hours. Any change in neurological exam, including development of a severe headache or nausea/vomiting, should prompt cessation of tPA and a stat head CT to evaluate for hemorrhage. Other rare side-effects to monitor for include orolingual angioedema, which is associated with prior ACE-inhibitor use and infarcts of the frontal and insular cortex, and anaphylaxis. All patients should receive a repeat noncontrast head CT after 24 hours to evaluate stability and absence of hemorrhage prior to starting antiplatelet or anticoagulant therapy.

Patients presenting with large, debilitating proximal infarcts of the internal carotid or proximal middle cerebral arteries should also be considered for endovascular thrombectomy with stent retriever technology. New evidence and 2015 AHA/ASA guidelines support the use of stent retrievers for this subset of patients if treatment can be initiated within six hours of symptom onset.[52] This is done in addition to tPA for all patients who are candidates to receive tPA and should not

Table 2. National Institutes of Health Stroke Scale (NIHSS)			
Level of consciousness	0 -alert	Motor function	0 - no drift
	1 - drowsy	Left leg	1 - drift before 5 seconds
	2 - obtunded	Right leg	2 - falls before 5 seconds
	3 - coma		3 - no effort against gravity
			4 - no movement
Orientation	0 - answers both questions correctly	Limb Ataxia	0 - no ataxia
	1 - answers one question correctly		1 - ataxia of 1 limb
	2 - answers no questions correctly		2 - ataxia of 2 limbs
Response to commands	0 - performs both tasks correctly	Sensory	0 - no sensory loss
	1 - performs one task correctly		1 - mild sensory loss
	2 - performs no tasks correctly		2 - severe sensory loss
Gaze	0 - no horizontal movements	Language	0 - normal
	1 - partial gaze palsy		1 - mild aphasia
	2 - complete gaze palsy		2 - severe aphasia
			3 - mute or global aphasia
Visual Fields	0 - no visual defect	Articulation	0 - normal
	1 - partial hemianopsia		1 - mild dysarthria
	2 - complete hemianopsia		2 - severe dysarthria
	3 - bilateral hemianopsia		
Facial Movement	0 - normal	Extinction/Inattention	0 - absent
	1 - minor facial weakness		1 - mild (1 sensory modality lost)
	2 - partial facial weakness		2 - severe (2 sensory modalities lost)
	3 - complete unilateral palsy		
Motor function	0 - no drift		
Left arm	1 - drift before 5 seconds		
Right arm	2 - drift before 10 seconds		
	3 - no effort against gravity		
	4 - no movement		

TABLE 2: NIH Stroke Scale Score

delay administration. Multiple randomized, controlled trials from 2010-2015 have shown improved functional outcome at 90 days with no significant increase in mortality or hemorrhage in patients treated with stent retrievers. The first and largest trial was MR CLEAN which enrolled 500 patients in the Netherlands and randomized them to receive usual care with or without endovascular intervention.[53] Functional independence, defined as a modified Rankin score of two or less, was higher in the treatment group with a number needed to treat of 7.4 (32.6% vs 19.1%, ARR 13.5%).[53] Four subsequent trials with similar protocols were stopped early once the data from MR CLEAN was published, and analysis of all trials suggests improved functional outcomes with use of stent retriever intervention in selected patients.[54]

In patients who receive tPA or endovascular intervention, aspirin should be held for the initial twenty-four hours, until repeat head CT is obtained. All other patients presenting with acute ischemic stroke should be started on full-dose aspirin within 24-48 hours of presentation. Early initiation of statin therapy after acute ischemic stroke is associated with improved discharge disposition and overall survival.[55] Statins have been shown to have benefits in addition to lipid-lowering ability, including plaque stabilization and neuroprotective effects. Supplemental oxygen is indicated only for patients presenting with hypoxia. Hyperthermia and hyperglycemia should be aggressively treated as persistence of such signs has been shown to worsen outcomes. Blood glucose should be consistently monitored and treated with insulin when above 180 mg/dL.[49]

The optimal strategy for management of blood pressure in the setting of acute ischemic stroke remains a heavily studied topic. There is theoretical improved perfusion of ischemic brain tissue with moderate hypertension, and early observational studies suggest a detrimental effect to lowering blood pressure in the initial twenty-four hours post infarct.[56] However, extreme hypertension also increases the risk of hemorrhagic conversion and may worsen cerebral edema. The COSSACS (Continue or Stop Anti-hypertensives Collaborative) trial suggests no harm but also no benefit with continuing patients on anti-hypertensives if already on these medications.[57] A recently published meta-analysis of thirteen randomized controlled trials involving more than 12,000 patients showed no difference in death, functional dependence, or recurrent vascular events at three months in those patients who were treated early with antihypertensives.[58] However, most of these studies enrolled patients fifteen or more hours after symptom onset. Therefore, more evidence is needed to determine the optimal strategy of blood pressure management during the hyperacute phase of stroke presentation, when the fate of the penumbra is likely most

influenced. "Permissive hypertension" remains the early goal for patients not receiving thrombolytics, and anti-hypertensives should be held at least for the initial 24 hours unless blood pressure exceeds a systolic of 220 mmHg or diastolic of 120 mmHg. In this scenario, blood pressure should be lowered by no more than 15%.[48]

Patients diagnosed with ischemic stroke should be placed on continuous telemetry for the initial twenty-four hours to screen for atrial fibrillation or arrhythmias which may suggest an embolic source of the stroke. Physical and occupational therapy should be consulted, and a formal evaluation of swallowing should be done prior to the initiation of feeding.[48] Early ambulation should be encouraged and prophylaxis through chemical or barrier methods should be taken to prevent deep venous thrombosis. Carotid doppler is recommended in patients presenting with ischemia corresponding to the territory supplied by the internal carotid arteries. While CT angiogram and MR angiogram are more sensitive studies for detecting significant carotid stenosis, these are less specific as an anatomical reduction in vessel diameter does not directly correlate with functional stenosis. However, angiographic studies are preferred over doppler when evaluating the posterior cerebral circulation. Carotid endarterectomy within two weeks of the index event is indicated for patients with non-disabling stroke and ≥ 50% ipsilateral stenosis by angiography, or ≥70% stenosis by non-invasive imaging if the surgical risk is deemed to be ≤ 6%.[59]

SECONDARY PREVENTION

Secondary prevention of ischemic stroke begins after confirmed ischemic stroke, TIA, and, according to the most recent guidelines, even clinically silent brain infarction.[60] In the past five decades, with development of strategies to prevent future strokes primarily through use of antiplatelet agents and better blood pressure control, the average rate of recurrent stroke in this population has reached an unprecedented low of approximately four percent.[61] Secondary prevention, similar to primary prevention, includes treatment of modifiable risk factors such as hypertension and hyperlipidemia, as well as initiation of antiplatelet therapy.

As opposed to the management of hypertension in primary prevention, the ideal agent used to manage blood pressure has been studied and does make a difference in outcomes. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) evaluated 6105 patients with a history of prior cerebrovascular event (TIA, ischemic or hemorrhagic stroke). This landmark double-blinded study randomized patients to one of three arms: placebo versus angiotensin converting enzyme (ACE) inhibitor alone versus an ACE inhibitor with a thiazide diuretic.[62] Regardless of preexisting hypertension, both groups of patients treated with antihypertensive agents showed benefit compared with placebo. Those patients treated with combination ACE inhibitor plus thiazide diuretic showed a 43% relative risk reduction compared with only 28% relative risk reduction in patients treated with ACE inhibitor alone, thus indicating a significant role of thiazide diuretics in the treatment of hypertension post-CVA. This finding was also verified in patient populations who had baseline systolic blood pressures < 140 mmHg.[63] In addition, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial included over 20,000 patients and confirmed no significant difference between ACE inhibitor versus placebo in reduction of recurrent ischemic stroke.[64] Ultimately, meta-analyses only showed significant risk reduction with the use of diuretics alone or in combination with ACE inhibitors, but not with ACE inhibitors alone, beta-blockers or calcium channel blockers alone in a compilation of trials.[65, 66]

Statins play a role both in the primary and secondary prevention of stroke. The largest and only statin trial to date dedicated solely to secondary prevention is the 2006 Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. In this prospective, randomized, placebo-controlled trial, 4731 patients with a history of stroke or TIA within the last one to six months with no known history of coronary heart disease and LDL levels between 100 and 190 mg/dl were randomized to high-intensity statin (atorvastatin 80 mg daily) versus placebo.[67] At five years, patients in the high-intensity statin group (versus placebo) showed a decrease in the primary end point, defined as the occurrence of fatal and nonfatal stroke [11.2 vs. 13.1%; 1.9% ARR] as well as a lower incidence of major cardiovascular events [14.1 vs 17.2%; 3.1% ARR). Notably, this study determined that the number of patients needed to treat for five years to prevent one stroke was only 46 patients (95% CI; 24-243), and the number of patients needed to treat for five years to prevent one major cardiovascular event was 29 patients (95% CI 18-75). This study did, however, show a small increase in the incidence of hemorrhagic stroke (2.3 vs. 1.44%; 0.86% absolute increased risk). Despite the above, there was no significant difference between treatment groups in overall mortality. These findings were re-emphasized in the ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults released in 2013.[34] The new guidelines mandated that all patients with "clinical ASCVD" defined as confirmed coronary cardiovascular disease, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin, be committed to high-intensity statin therapy, defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg, until the age of 75 years and beyond regardless of baseline cholesterol status.

The third major tenet of secondary prevention of stroke includes the use of antiplatelet therapy. There are currently three agents recommended in the AHA guidelines for secondary ischemic stroke prevention: aspirin 50-325 mg, combination aspirin/extended release dipyridamole or clopidogrel monotherapy.[60] According to a 1999 meta-regression analysis of eleven placebo controlled trials, aspirin alone reduces the risk of recurrent stroke by 15% consistently across a wide range of doses.[68] The first trial to compare clopidogrel to aspirin was the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, which which found that clopidogrel was non-inferior to aspirin in the rates of stroke, myocardial infarction and vascular death in patients with known atherothrombotic disease.[69] Subsequently, the robust Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial demonstrated similar rates of stroke, myocardial infarction or vascular death in clopidogrel when compared with combination of aspirin and extended-release

dipyridamole.[70] Comparison of adverse events was significant for similar rates of occurrence of intracranial hemorrhage; however combination aspirin and extended-release dipyridamole had an increased risk of gastrointestinal hemorrhage. The Management of Atherothrombosis With Clopidogrel in High-Risk patients with TIA or Stroke (MATCH) trial studied over 7500 patients to compare use of combination clopidogrel plus aspirin with aspirin alone in patients with prior stroke or TIA.[71] Conclusions of the study found that the combination of aspirin plus clopidogrel offered substantially increased risk of bleeding without benefit for stroke prevention. These findings have been confirmed by several trials since that time including the Secondary Prevention of Small Subcortical Strokes (SPS3) trial which was terminated early and published in 2012 confirming an increased risk of major bleeding with use of combination dual antiplatelet therapy with no added benefit for primary secondary prevention.[72]

Aspirin is the only antiplatelet agent that has been accepted as effective for the hyperacute treatment of acute ischemic stroke within 48 hrs.[48] Recently, the CHANCE trial became the first major published trial directly comparing aspirin and clopidogrel versus aspirin alone for treatment of low risk ischemic stroke (NIHSS ≤ 3) or high risk TIA ($ABCD^2$ for Age, Blood pressure, Clinical features, Duration of symptoms, and Diabetes; score of ≥ 4).[73] This study involved 5170 Chinese patients who all received aspirin 75 to 300 on day one and then were randomly assigned clopidogrel and aspirin (clopidogrel 300 mg loading dose, then 75 mg daily for 90 days, plus aspirin 75 mg daily for the first 21 days) or aspirin plus placebo (75 mg daily for 90 days).[73] At ninety days, there was a significant 3.5% absolute risk reduction in recurrent stroke in the aspirin plus clopidogrel arm compared with aspirin plus placebo. Additionally, the risk of bleeding and rate of hemorrhagic stroke was low and equal in both groups. These findings have been extrapolated to the general population and have been validated by the recent update in guidelines advocating use of combination aspirin and clopidogrel for use within the first 24 hours and for 21 days after minor ischemic stroke or TIA.[48]

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