Chronic Management of Blood Pressure After Stroke
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Case
A 70-year-old, right-handed African American woman with diabetes mellitus, treated with an oral hypoglycemic, and untreated mild hypertension developed right-sided face, arm, and leg weakness while at home preparing breakfast. She was able to reach the telephone and dial 911. An ambulance was summoned, and the Emergency Medical Service team, on arrival, noted a right facial droop, dysarthria, and right-sided weakness. She was transported to a local hospital, arriving within an hour of the onset of the event. The hospital stroke team was consulted and initiated an evaluation.

Physical Examination
The patient was afebrile, with a pulse of 72 and a blood pressure of 170/90 mm Hg. Neck was supple with no carotid bruits. Temporal arteries were nontender. Heart was regular with no murmurs or gallops. Peripheral pulses were 2+, and capillary refill was good. There were no peripheral bruits.

Neurological Examination
She was awake, lucid, alert, and well oriented. She did not report headache. Speech was dysarthric, but comprehension was good and she spoke in fully formed sentences. There was no sensory neglect or extinction. Cranial nerve examination revealed normal, reactive pupils and full visual fields; fundoscopic examination disclosed grade I hypertensive changes. She had a flattened nasolabial fold on the right, but was able to close her eyes and wrinkle her forehead. Motor examination revealed impaired fine motor movements in the right hand, pronator drift of the outstretched right arm, and mild proximal weakness of the right leg; sensory examination revealed decreased vibratory sensation in the distal feet bilaterally. Tendon reflexes were brisk in the right arm; ankle jerks could not be elicited. Plantar response was flexor bilaterally. Coordination in the arms and legs was normal, allowing for proximal weakness. Gait was not tested.

Laboratory Studies
A complete blood count, chemistry profile, coagulation studies, and cardiac enzymes and erythrocyte sedimentation rates were obtained, and were remarkable only for a blood glucose of 175 mg/dL and a sedimentation rate of 20 mm/h. EKG revealed a normal sinus rhythm, with evidence for left ventricular hypertrophy by voltage criteria and nonspecific ST changes. Brain computed tomography (CT) scan revealed age-appropriate atrophy and several small, old, deep white matter infarcts, but no acute changes or bleeds.

Subsequent Course
Based on the acute presentation, the distribution of deficits, and the CT findings, a diagnosis of acute cerebral ischemia was made. There were no contraindications to acute thrombolytic therapy, and with the patient’s informed consent after education regarding potential risks and benefits, intravenous tissue plasminogen activator was administered. Subsequent evaluation for the etiology of the stroke included carotid duplex studies and magnetic resonance angiogram of the cervical and intracerebral vessels, which revealed findings consistent with a left internal carotid artery occlusion at the bifurcation. An acute, small deep border zone infarction corresponding to and explaining the acute focal neurological deficit was seen on diffusion-weighted images on MRI scan of the brain. Transthoracic echocardiogram revealed no obvious intracardiac source for embolism.

Her neurological status improved substantially over the next several days, leaving her with residual fine-motor impairment of the right hand and a mild facial droop. Formal Mini-Mental State score was 30/30. She was placed on aspirin 81 mg/d and educated in cardiovascular disease warning signs as well as risk factor management, including the American Diabetes Association1,2 and National Cholesterol Education Program3 recommended programs for control of diabetes and lipid disorders. Blood pressure on discharge was 160/95 mm Hg.

Discussion
This 70-year-old woman with diabetes and untreated hypertension presents with a first symptomatic ischemic stroke. Her physical examination and cardiac studies show evidence of chronic changes caused by hypertension, and the CT is suggestive of small-vessel disease related to hypertension and diabetes. Stroke, which is the third leading cause of death in the United States, is strongly linked to elevation of blood pressure.4,5 All forms of hypertension (isolated systolic, diastolic, or combined systolic and diastolic) are associated with stroke risk, and the relationship between hypertension and stroke is consistent among diverse geographic regions and ethnic groups.6,7 Unfortunately, hypertension awareness, treatment, and control remain less than optimal,8 as was the

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case in this patient, and high stroke mortality rates parallel high prevalence of hypertension and relatively low medication treatment proportions for hypertensive people in different countries. Although observational epidemiological studies and clinical trials provide firm evidence that lower baseline blood pressure and active lowering of blood pressure are associated with reduced stroke risk, we continue to witness an evidence-based practice gap regarding blood pressure control in the community for secondary as well as primary prevention.

The very compelling evidence that first stroke can be averted by blood pressure control is now substantiated for recurrent stroke. Important practical questions remain, however, for the practicing physician regarding the chronic management of blood pressure after stroke. How soon after stroke is it safe to start blood pressure lowering medication? Which class of blood pressure lowering agents should be used? Is it the blood pressure lowering effect itself that reduces stroke risk, or some other property of the agent? What is the target for blood pressure lowering in the chronic stroke patient? Is lower blood pressure better or will this result in recurrent stroke? Finally, once there is dementia or cognitive impairment, should one elevate or lower blood pressure? We attempt to address these questions in the context of the aforementioned case.

When Is it Safe to Administer Blood Pressure Lowering Therapy After Acute Stroke?

The patient had a blood pressure of 170/90 on presentation and 165/95 on discharge, with substantial recovery of function in the days following her stroke. Issues related to the timing of blood pressure lowering therapy in the acute phase of stroke have been extensively addressed in a prior issue of this journal. There remain no definitive data to guide decisions regarding this issue; informal discussion with experts suggests that the optimum time period for starting antihypertensive therapy after acute ischemic stroke may be as early as 7 days (possibly earlier), and as long as a month or more. Administration of blood pressure lowering medication began on the seventh day after the acute ischemic stroke in our patient, because her neurological deficits had improved and she appeared medically stable. Compliance may be improved by initiating treatment before hospital discharge or shortly thereafter in juxtaposition to the acute event, when the patient may be most highly motivated to follow preventive recommendations.

What Is the Target Blood Pressure Goal, and How Soon Should This Goal Be Reached?

Our patient presented with a blood pressure in the “hypertensive” range as defined by criteria in the 6th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI); however, even milder degrees of blood pressure elevation may pose increased risk for cardiovascular events. Both observational and randomized clinical trials demonstrate a positive, direct log-linear association between diastolic blood pressure and stroke risk; stroke risk rises linearly with increased blood pressure, with no clear threshold marking an acute dramatic increase in risk. In fact, the majority of patients with incident stroke have stage 1 hypertension or “high normal” blood pressure according to prior studies using the JNC VI classification. This suggests that we may need to shift our conceptual focus from hypertension as defined by threshold criteria to concern with the magnitude of the blood pressure level itself. This concept is further highlighted by Lewington et al’s demonstration that the risk of vascular disease mortality increases in a continuous manner beginning as low as 115/75 mm Hg (the lowest category of systolic blood pressure studied), with an approximate doubling of risk with each incremental increase in blood pressure of 20 mm Hg systolic or 10 mm Hg diastolic.

A precise target blood pressure goal for prevention of recurrent stroke has not been established according to clinical trial data. Aside from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), to date there has been no large-scale clinical trial of blood pressure lowering among stroke patients where recurrent stroke as the primary outcome end point was investigated. PROGRESS showed that with meticulous lowering of blood pressure, in this case using combination therapy with an angiotensin-converting enzyme (ACE) inhibitor (perindopril) plus a thiazide-like diuretic (indapamide), across-the-board reductions in total stroke, fatal or disabling stroke, nonfatal or disabling stroke, nonfatal myocardial infarction, and other important stroke-related outcomes could be achieved. The main results held true for those with or without a history of hypertension. The major benefit occurred in the combination therapy group where the mean blood pressure lowering was ~12/5 mm Hg; this may have been the result of greater blood pressure reduction in this group. The perindopril-alone treatment group, with mean blood pressure reductions of 5/3 mm Hg, showed trends for favorable effects not reaching statistical significance.

The Heart Outcomes Prevention Evaluation (HOPE) trial was designed to study the effects the ACE inhibitor ramipril in persons at high risk for cardiovascular disease. In HOPE, blood pressure was lowered by ~3/2 mm Hg in the ramipril treatment group compared with placebo. There was a statistically significant reduction of many important cardiovascular disease outcomes including stroke, with beneficial effects in hypertensives and nonhypertensives as well as other subgroups of patients. Among study subjects with a prior history of stroke or transient ischemic attack (n=1013), the relative risk was consistent with a benefit for stroke reduction for the ramipril treatment group, but this did not reach statistical significance. Although the documented office blood pressure reductions in the HOPE study were modest, a subsequent substudy found substantial and significant differences between treatment and placebo groups with ambulatory blood pressure monitoring, suggesting that the office blood pressure values reported in the main study may not have adequately captured the magnitude of the blood pressure lowering effect in the treatment group.

In the absence of large-scale clinical trial data needed to help establish blood pressure lowering targets for prevention of recurrent stroke, utilization of the 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) targets seems reasonable. This translates to a target blood pressure of <140/90 mm Hg for most stroke patients and <130/80 mm Hg for patients with diabetes...
mellitus or chronic kidney disease. Beyond these goals it is difficult to know with certainty how much lower to target the blood pressure and whether lower blood pressures would be safe and effective. The Hypertension Optimal Treatment (HOT) trial found that whereas lowering hypertensive patients’ blood pressure to a systolic of 140 mm Hg and a diastolic of 85 mm Hg or lower reduced cardiovascular events, further reduction to 120 mm Hg systolic and 70 mm Hg diastolic added little benefit, but did not cause significant harm.23

Many hypertensive patients will require more than one antihypertensive medication to achieve target blood pressure; African Americans, among others, are at particularly increased risk for hypertension and associated complications.24 In patients with blood pressure 15 to 20 mm Hg systolic or 10 mm Hg diastolic above the target goal of 140/90 mm Hg, more than one agent is often ultimately needed,22,24 and consideration may be given to institution initially of combination therapy, with careful titration and close monitoring.

Our patient, with the additional cardiovascular risk factor of type 2 diabetes, had a target blood pressure of <130/80 mm Hg according to JNC 7. She was discharged with a blood pressure of 165/95. How rapidly should one aim to achieve the target goal? Observational epidemiological studies suggest that blood pressure is a predictor of both early and late recurrent stroke.25 However, we lack substantial data to guide us as to the rapidity of blood pressure control. PROGRESS had a very broad eligibility window since the time from entry stroke; however, active treatment was equally effective when data were stratified according to entry <6 months versus 6 months to 5 years.18 These data do not establish the earliest effective time for treatment beyond a crude cutoff point at <6 months. We therefore recommend following the JNC 7 guidelines for follow-up and monitoring blood pressure control, with follow-up and adjustment in uncomplicated patients at approximately monthly intervals until blood pressure reaches goal, and then at 3- to 6-month intervals thereafter;22 reaching the target blood pressure within a 3- to 6-month interval is a reasonable goal. Patients with stage 2 hypertension (≥160 systolic or ≥100 diastolic mm Hg) and those with other complicating comorbidities may need more frequent interval visits at the discretion of the treating physician.

Which Agent or Agents Is Most Effective for Prevention of Recurrent Stroke, and Is it Blood Pressure Lowering or Some Other Mechanism That Underlies the Beneficial Effect? Unquestionably, lower usual blood pressure and active lowering of blood pressure are associated with a reduction of stroke incidence.4 The predicted degree of blood pressure lowering (eg, 5 to 6 mm Hg lowering in usual diastolic blood pressure) associated with fewer strokes (35% to 40% fewer) in observational studies15,16 nicely approximates the reduction of stroke risk observed with blood pressure lowering in clinical trials. Overview analyses suggest that all major classes of blood pressure lowering agents (ie, diuretics, β-blockers, calcium-channel blockers, and ACE inhibitors) lower primary stroke risk.26-27 It has been suggested that calcium-channel blockers may provide more protection from stroke than from risk for myocardial infarction. A single study showed that fatal and nonfatal stroke were more common with captopril, an ACE inhibitor, than with a diuretic and β-blocker therapy;28 these results may, in part, be explained by higher baseline and follow-up blood pressure levels in the captopril treatment group.11 Chapman and Neal11 have concluded that the choice of a blood pressure lowering agent for prevention of first stroke appears to be somewhat irrelevant, unless there are compelling indications for a certain class of agents, namely, randomized trials demonstrate efficacy for all major blood pressure lowering agents, absolute benefits vary by baseline risk (with large benefits seen in elderly patients, diabetic patients, severe hypertensive patients, and patients with multiple risk factors or established vascular disease), high-risk nonhypertensives benefit, and, finally, the magnitude of the blood pressure reduction itself appears to be the key factor. Although recently published studies of ACE inhibitors and angiotensin receptor blockers in cardiovascular disease prevention have fueled the ongoing debate concerning the contribution of blood pressure lowering versus pleiotropic or nonblood pressure lowering effects,29-33 the absolute magnitude of blood pressure reduction continues to appear as the dominant factor in risk reduction.

A recent metaanalysis34 found that all classes of agents studied reduced risk of stroke and composite cardiovascular events, including stroke, coronary heart disease, heart failure, and cardiovascular death. Although there were nonsignificant trends toward greater efficacy of calcium-channel blockers over β-blockers and diuretics and for greater efficacy of these agents over ACE inhibitors in stroke, these trends may have reflected greater blood pressure lowering in the former agents, and independent analyses of the magnitude of blood pressure reduction revealed strong and significant benefits for greater blood pressure reduction.

Thus far, we can conclude that although certain classes of blood pressure lowering agents such as ACE inhibitors may possess unique properties not mediated by blood pressure lowering effects, there is not yet substantial proof that their mechanism of action definitively goes beyond blood pressure lowering for stroke prevention.6 Aggressive blood pressure lowering, therefore, remains an important theme for stroke prevention.

Our patient had diabetes mellitus uncomplicated by proteinuria or microalbuminuria. Antihypertensive therapy with the combination of perindopril with indapamide, shown to be effective in the PROGRESS trial,18 is a reasonable regimen; comparative studies with other agents or regimens, which may be equally or more effective in secondary prevention of stroke, are lacking at this time. Because of concern that diuretics may be associated with hypokalemia and its associated cardiovascular morbidities, monitoring for hypokalemia and appropriate supplementation is prudent.

Will Blood Pressure Lowering Result in Recurrent Stroke? Physicians have expressed concern that lowering of blood pressure, especially in elderly people, could result in cerebral hypoperfusion and stroke, particularly if there is focal or multifocal occlusive cerebrovascular disease. Contrary to these predictions, lowering of blood pressure, in fact, results
in stroke risk reduction, as has been demonstrated in the Systolic Hypertension in the Elderly Program (SHEP), the Systolic Hypertension in Europe (Syst-Eur) Trial, and the Swedish Trial in Old Patients with Hypertension (STOP).\textsuperscript{35–37} Overall, in these studies, reasonable blood pressure lowering did not lead to stroke or hypotension-related symptoms. However, individual variation in response to blood pressure lowering exists, and this must be taken into consideration when titrating blood pressure to a target goal in an individual patient. Most patients will tolerate lowering of blood pressure if it is done slowly, with close monitoring of neurological status.

**Should Blood Pressure Be Lowered Once There Is Cognitive Impairment or Dementia?**

Several studies have shown that administration of blood pressure lowering agents is associated with lower risk of dementia. In the Syst-Eur Trial, using the long-acting calcium-channel blocker nitrendipine, the extended follow-up (median 3.9 years) phase study showed that long-term antihypertensive therapy reduced the risk of dementia by 55\%, with an estimated 20 cases of dementia prevented per 1000 patients treated for 5 years.\textsuperscript{38} Both Alzheimer disease and mixed or vascular dementia were reduced. The PROGRESS trial demonstrated a significant reduction in cognitive decline (defined as a decrease in 3 points on the Mini-Mental State examination) and eventual dementia in actively treated patients who went on to have a recurrent stroke; these treatment effects were not seen in the absence of recurrent stroke\textsuperscript{39} and may reflect an increased risk for dementia seen in association with stroke.\textsuperscript{40}

Once there is cognitive impairment or dementia, a net benefit in prevention of further cognitive impairment with administration of antihypertensive agents is less clear.\textsuperscript{41} One observational study of patients with multiple cerebral infarcts with or without dementia\textsuperscript{42} found elevated systolic blood pressure in the patients with dementia to be a protective factor against further cognitive decline or progression to dementia. Another study of risk factor control in patients with multi-infarct dementia found that whereas control of systolic blood pressure in the 135 to 150 mm Hg range was associated with improved cognition, lower systolic blood pressure was associated with deterioration of cognitive function.\textsuperscript{43}

Our patient had no history of cognitive dysfunction and had a normal Mini-Mental State examination at discharge. We therefore recommended blood pressure lowering to a target of $<130/80$ mm Hg in accordance with JNC 7 guideline targets for people with diabetes mellitus.

**Conclusion**

Compelling evidence exists for multiple beneficial effects of blood pressure lowering in patients at risk for ischemic stroke, with decreased risk of new or recurrent stroke and other cardiovascular complications, and potentially decreased risk of both vascular and nonvascular dementia. Although the mechanism of this protective effect is not entirely clear and more than one effect of antihypertensive medications may be relevant, lowering of blood pressure itself confers significant benefit in all populations studied and should be assiduously pursued. Although particular classes of antihypertensive agents may be indicated for special populations based on other comorbidities, large-scale studies show beneficial effects with all classes of agents used, and choice of agent may be guided by individual patient characteristics. Certain populations with baseline blood pressure levels $\geq 15$ to $20/10$ mm Hg over the target goal may require therapy with more than one agent. Precise target blood pressure levels for patients with stroke have not been delineated, but large-scale studies suggest that lower target blood pressure levels may confer commensurately greater benefit with minimal additional risk; further studies are needed to guide management in patients with pre-existing multi-infarct dementia. Lacking specific guidelines for blood pressure lowering in the setting of ischemic stroke, we recommend following the JNC 7 guidelines for medical management of hypertension. Further controlled studies investigating the optimal time window after ischemic stroke for institution of blood pressure lowering therapy and the optimum rate of blood pressure lowering to target are needed to guide evidence-based therapy.

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