Recommendations for Hypertension Management in relation to STROKE

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Background

Stroke should be conceptualized as a syndrome. The term ‘stroke’ is a rubric that includes ischemic stroke and transient ischemic attack, intracerebral hemorrhage, atraumatic or aneurysmal subarachnoid hemorrhage and cerebral venous sinus thrombosis. Each of these stroke types has very different prognoses, treatment and outcomes. Hypertension is quantitatively the most important risk factor for stroke. It is relevant as a risk factor for all stroke types except cerebral venous sinus thrombosis (which will not be discussed further).

Ischemia is the most common stroke type comprising 65-85% of strokes depending upon geographical location in the world (relatively more ischemia in the west and more hemorrhage in the east). Both TIA and ischemic stroke should be thought of as ischemic stroke syndromes since the mechanisms and risk factors are identical. Hemorrhagic stroke syndromes comprise 15-35% of all strokes and are roughly evenly divided between intracerebral hemorrhage and atraumatic subarachnoid hemorrhage. It is clinically impossible to reliably distinguish between ischemia and hemorrhage based upon clinical factors alone; imaging is required. Thus, all patients presenting with an acute stroke syndrome require urgent brain imaging.

A majority (~70%) of stroke patients have a known prior history of hypertension. However, hypertension is of variable importance depending upon stroke type. Hypertension is most important as a risk factor for intracerebral hemorrhage. Its effect size as a risk factor for subarachnoid hemorrhage is much smaller where tobacco smoking and family history are more important. Because ischemic stroke has a myriad of causes, hypertension is variably important in subarachnoid hemorrhage, depending upon mechanism. Classically, the subtypes of ischemic stroke are defined by mechanism; broad categories include cardioembolism, large artery atherosclerotic disease, lacunar stroke and undetermined causes. For example, as a precursor to atrial fibrillation, to atherosclerotic disease and to small vessel lipohyalinosis, hypertension is an important underlying cause respectively of cardioembolic, arteroembolic and lacunar stroke. By contrast, hypertension is less relevant when the cause of stroke is cardioembolic due to endocarditis. However, broadly, because the major mechanisms of stroke (lacunar, cardioembolic, large artery) are commonly preceded by longstanding hypertension, hypertension is the most important risk factor for ischemic stroke.

Most stroke patients present to hospital with elevated blood pressures. Management of hypertension among stroke patients can be naturally divided into the acute phase (first 72h) and the chronic phase. In general, there is a dearth of available data to guide therapeutic decision-making around blood pressure management in the acute phase, and much better data to guide therapy in the chronic, stable phase.
**Approach to Management of Elevated BP in Acute Stroke**

In ischemic stroke, there is a substantial theoretical concern that induced hypotension could worsen brain ischemia. Physiological data confirmed by imaging suggest that in the face of persistent arterial occlusion, either intracranial or extracranial, hypotension can make things worse. Even in lacunar stroke due to small penetrating arterial occlusion, proof of a perfusion deficit is clearly associated with worse outcomes. In contrast, cohort studies suggest that induced hypertension may be beneficial. At both extremes, elevated BP and very low BP are poor prognostic factors after stroke. In general, patients with elevated blood pressure in the acute phase of stroke will show a gradual decline in blood pressure over 48 hours. The vast majority of the time, elevated BP appears to be reactive to stroke rather than the cause. The concept of malignant hypertension defined by neurological dysfunction is uncommonly true; more often, stroke results in elevated blood pressure rather than elevated blood pressure resulting in stroke. Overall, there is a paucity of data about what do in the acute phase. Thus, current recommendations for treatment are based upon a consensus of experts.

Reduction of extreme blood pressure elevation (eg. Systolic BP > 220 or diastolic BP > 110 mmHg) by 25% over 24 hours is likely to be generally safe. It remains unclear if this is beneficial and it is physiologically likely that any benefit is limited to those patients who have reperfused spontaneously or after intervention. Safety data from early studies of thrombolysis led to the notion that BP > 185/110 should be treated both before, during and after thrombolysis to reduce the risk of secondary intracerebral hemorrhage. However, there are no randomized data to support this choice of threshold. It has simply been historically accepted in all thrombolytic studies that this approach is warranted.

In intracerebral hemorrhage, there are clear data to show that reductions in blood pressure of 25% or more in the first 24 hours are safe. Perfusion imaging shows no substantial reduction in brain perfusion in the peri-hematomal region. Further, diffusion imaging fails to show any evidence of ischemia. Preliminary data suggest that reduction in blood pressure results in reduced growth of hematoma. This is highly relevant because the volume of hemorrhage is a very strong predictor of final outcome and hemorrhage growth in the first 24 hours is a potential surrogate marker for clinical outcome.

A pilot study in ICH, the INTERACT pilot study has been completed. With 404 patients, it appears that blood pressure lowering is relative safe and may lead to reduced hematoma growth. A large multi-national randomized trial of blood pressuring lowering in acute ICH is now underway.

No substantial randomized data on acute blood pressure management exist for aneurysmal subarachnoid hemorrhage. Case series evidence suggests that early anti-hypertensive therapy will reduce the risk of early re-bleeding. Later, after treatment of the aneurysm, hypertensive therapy may be required to manage vasospasm. Treatment is currently based upon common practice and is not guided by randomized clinical trials.

**Approach to Secondary Prevention after Stroke**

After the acute phase of stroke, it is very clear that hypertension should be treated to prevent
recurrence. The PROGRESS trial\textsuperscript{8} clearly demonstrated that reduction in blood pressure, among patients with past stroke (ischemic or hemorrhagic types) clearly reduced the risk of recurrent stroke events. The effect was largest among patients with past intracerebral hemorrhage. Definite targets for stroke are not defined and the role that BP reduction plays according to stroke type remains to be determined.

The ACCESS pilot study\textsuperscript{9} (n=334) examined patients with acute stroke, without carotid artery occlusion or stenosis, and randomized them to received candesartan or placebo for one year. A positive result was observed for candesartan in the reduction of mortality and vascular events at 1 year. The survival curves diverged well after the acute phase of stroke and it remains unclear how to explain the mechanism of this result. Further studies are ongoing.\textsuperscript{10}

The SPS3 study, which is ongoing, is examining patients with lacunar stroke and small subcortical infarcts. Almost all such patients have underlying hypertension. Patients are randomized to two different antiplatelet regimens and in a factorial design to a normal BP target (systolic BP < 150 mmHg) or aggressively lower BP target (systolic BP < 130 mmHg).\textsuperscript{11, 12}

In general, the choice of agent to treat hypertension in the secondary prevention of stroke is likely irrelevant. In the PROGRESS trial, a combination of diuretic and ACEi was used and it is on this basis that guidelines recommend the use of this combination. In primary prevention, diuretics remain the first choice agent and on this basis many have extrapolated a diuretic-first approach to secondary prevention. Many stroke patients have other concurrent reasons to guide choices of therapy (eg. Diabetes mellitus, congestive heart failure, atrial fibrillation or coronary artery disease). Where there are no compelling indications for specific agents, the type of stroke cannot guide pharmacologic choice. Simply achieving blood pressure control is the goal.

![Graph from PROGRESS.][8]
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Approach to the Primary Prevention of Stroke

Most trials of antihypertensive agents in primary prevention have shown that the prevention of stroke is the main driver of the usual composite outcome. ALLHAT confirmed that diuretic therapy remains a robust first choice for prevention of stroke.13 As in secondary prevention, achieving blood pressure lowering remains the primary goal, rather than a specific choice of agent.

Primary Prevention of Vascular Dementia

There is a strong relationship between hypertension and small vessel white matter ischemic disease (SVID) in the brain. It has been shown convincingly that magnetic resonance (MR) defined T2-hyperintense lesions in the white matter are most commonly due to tiny regions of ischemia or ischemic demyelination. These lesions are prevented or reduced with control of blood pressure, are strongly associated with the clinical phenotype of dementia. The ‘Nun’ study has convincingly demonstrated that the neuropathological changes of Alzheimer’s disease act synergistically with stroke to cause clinical dementia.14 15

Treatment of hypertension, particularly early in life, is likely to prevent or delay incident dementia. There are some preliminary data to suggest this to be the true, but the data are not fully convincing at this point. Measurement of dementia in studies of hypertension have not been optimal; for example, the use of the mini-mental status examination (MMSE) to define dementia is particularly problematic. Additionally, the duration of follow-up has been too short. Nevertheless, a meta-analysis including randomized trials of primary prevention suggests that treatment reduces incident dementia.16

![Figure 3: Forest plot of placebo-controlled trials of antihypertensive treatment that assessed incident dementia](Image)

From HYVET-COG.[16]
Implications

Stroke is a multifaceted condition where hypertension is the principal risk factor, accounting for 30-40% of the population attributable risk globally. Treatment of hypertension has the potential to substantially reduce the burden of neurovascular disease including vascular dementia on the global population. Much remains to be learned about the acute treatment of hypertension and the best choice of agents for treatment in the chronic phase. It is urgent that randomized trials be funded to study the treatment of hypertension in stroke.

References


8 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033-41


