Blood Pressure Reduction for Vascular Risk
Is There a Price To Be Paid?

Jonathan Birns, BSc, MRCP; Hugh Markus, DM, FRCP; Lalit Kalra, MD, PhD, FRCP

Abstract—The importance of lowering blood pressure (BP) in hypertensive subjects is well-known and recent studies suggest that lowering of BP in patients who may already be in the normotensive range further reduces the risk of vascular events, particularly stroke. Epidemiological data have also shown that lower BP and antihypertensive treatment may be associated with cognitive impairment once cerebrovascular disease is established. However, the relationship between hypertension and cerebrovascular disease is more complex than suggested by epidemiological or intervention studies. Cerebral imaging studies have shown that cerebral blood flow (CBF) is reduced in areas of small-vessel disease (SVD) and the degree of hypoperfusion correlates with disease severity. Furthermore, impaired neuropsychological performance has been found to correlate with cerebral hypoperfusion in patients with established SVD. These findings raise questions surrounding the desirability of lowering of BP beyond a certain level in such patients. It is conceivable that indiscriminate BP reduction may compromise cerebral perfusion and function in these patients, increasing the risk of cognitive decline and cerebrovascular disease progression. Randomized clinical trials addressing the relationship between antihypertensive treatment and vascular cognitive impairment are lacking. Further studies are therefore needed to assess the cognitive consequences of BP reduction in people with established cerebrovascular disease. This will help to direct appropriate protective strategies and treatments in a vulnerable group of people, many of whom have hypertension and cerebrovascular disease at the same time. (Stroke. 2005;36:1308-1313.)

Key Words: cerebrovascular disorders ■ cognition ■ hypertension

The role of hypertension in the cause of vascular disease and the beneficial effects of antihypertensive treatment in preventing cardiac disease and stroke are well known.1 Recent studies suggest that the benefits of lowering blood pressure (BP) are independent of the initial level and that further reductions, even within the normotensive range, protect against future vascular events. This has led to a move away from using thresholds of BP to determine treatment and toward a policy favoring antihypertensive treatment in all those considered to be at high vascular risk. Recent studies have suggested that “lower is better” for BP control as a goal in reducing vascular risk.2–4 This evidence of benefits from BP reduction comes from large randomized controlled trials designed to prevent stroke, myocardial infarction, and other vascular events. Although randomized controlled trials remain the gold standard for determining the effectiveness of interventions, it is important to remember that these are clinical intervention studies based on epidemiological observations. Their scope is limited by the choice of primary and secondary endpoints, limitations imposed by patient selection criteria, and the number of prespecified analyses that can be undertaken within the sample. Hence, although the guidelines suggested by these studies may be applicable to the majority of patients at risk, there may be a subgroup of patients in whom the benefits of vascular event reduction are associated with morbidity in areas not addressed in the randomized controlled studies. A particularly vulnerable group may be patients with long-standing hypertension who have significant cerebral small-vessel disease (SVD), in whom aggressive antihypertensive treatment may have adverse effects on cerebral perfusion and, hence, cognitive function.

Cerebral SVD
SVD accounts for one-quarter ischemic strokes5 and is probably the most common cause of vascular cognitive impairment.6 It can cause both discrete regions of lacunar infarction and more diffuse ischemic changes in the periventricular and deep white matter called leukoaraiosis. On pathology, thickening and hyaline deposition of the small arterioles supplying the white matter can be seen and, in some cases, localized small-vessel microatheroma at the origin of the deep perforating arteries has been noted.7 Pathophysiologically, it is thought that a diffuse arteriopathy of the cerebral small vessels results in hypoperfusion and impaired autoregulation, and subsequent ischemia. If acute, this causes...
small focal regions of damage in perforating arteriole territories (lacunar infarction), whereas if it is more chronic it results in diffuse ischemic injury (leukoaraiosis).5

**Perfusion of the Brain**

The supratentorial brain exhibits a number of distinct patterns of vascular supply, offering relative protection from circulatory changes. However, the deep brain structures (white matter and deep gray nuclei) are supplied by perforating arteries that are end-arteries with no collateral supply. These penetrating arteries do not arborize but give-off perpendicularly oriented short branches that irrigate the white matter, each of which provides the blood supply to a cylindrically shaped metabolic unit. The arrangement of white matter metabolic units is such that one distributing vessel irrigates only one metabolic unit. In the region between the cortical and ventricular surfaces, which includes the centrum semiovale and basal ganglia, centripetal and centrifugal arteries form an internal watershed area particularly susceptible to being injured as a result of systemic or focal decreases in cerebral blood flow (CBF).6 Hence, the centrum semiovale, basal ganglia, and subcortical white matter are the most common sites for lacunar infarcts as the penetrating arteries undergo arteriosclerotic change because of age, hypertension, and diabetes mellitus.9

Chronic, episodic ischemic injury in the deep areas of the brain does not always result in infarction but produces many combinations of neuronal and glial damage that are intermediate between the extremes of infarction and focal neuronal loss with varying degrees of loss of myelin and axons, reactive astrogliosis, and tissue rarefaction.10 The radiological correlate of these pathological changes is leukoaraiosis demonstrated by hypointensities on computed tomography scanning, or hyperintensities on T2-weighted magnetic resonance imaging scanning. Quantitative perfusion magnetic resonance imaging studies have shown that CBF is reduced in the periventricular areas in patients with leukoaraiosis and the degree of hypoperfusion correlates with the severity of leukoaraiosis.11

**Clinical Consequences**

Lacunar infarction results in clinical syndromes such as pure motor stroke and pure sensory stroke characterized by the absence of cortical features such as dysphasia. Subcortical ischemia may also result in cognitive impairment and dementia, and gait apraxia that may be subtle and insidious in onset. These clinical manifestations result from disruption to subcortical–frontal systems, in particular dorsolateral prefrontal–subcortical circuits.12 The characteristic neuropsychological profile of cerebral SVD includes early impairment of attention and executive function (encompassing volition, planning, purposive action, and effective performance), with slowing of motor performance and information processing.6 This is confirmed in studies that have shown subcortical gray and white matter hyperintensity volumes and scores on white matter rating scales on magnetic resonance imaging to correlate significantly with executive dysfunction in different patient populations.13 Because episodic memory is relatively spared compared with other causes of cognitive impairment, neuropsychological impairments resulting from SVD are not readily identified by commonly used measures of cognitive impairment. A number of studies have shown that attention and processing speed tests and assessments of executive function are better at discriminating patients with subcortical vascular cognitive impairment from controls or those with other forms of cognitive impairment.13,14

**Hypertension and Psychomotor Dysfunction**

Evidence regarding the effects of BP on cognitive performance remains controversial. As shown in Table 1, cross-sectional studies demonstrate conflicting relationships between cognitive function and BP. This picture is further confounded by longitudinal studies that show that elevated BP in midlife is associated with a higher prevalence of white matter injury and cognitive decline in later years, but lower BP in old age is also associated with poor cognitive function.22,31–34 These data suggest a complex and dynamic relationship between BP and cerebral function: high BP may initially accelerate arteriosclerotic change and impair cerebral autoregulation with adverse effects on cognition, but high BP may be required for adequate perfusion when arteries are diseased and cerebral autoregulation is impaired. However, cross-sectional data may be misleading because of known and unknown confounding factors and data from longitudinal studies may be very time-dependent. Observational studies may demonstrate associations but do not determine causality, the latter only being shown by intervention studies that may present ethical difficulties.

The effect of antihypertensive treatment on cognitive function is also a matter of debate. Only a few completed randomized controlled clinical trials of BP-lowering agents have reported the effects of treatment on the risk of cognitive impairment (Table 2). The Syst-Eur trial demonstrated active treatment with nitrendipine with or without enalapril and/or hydrochlorothiazide to reduce the incidence of dementia by 50% from 7.7 to 3.8 cases per 1000 patient-years.40 The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Study showed cognitive decline to occur in 9.1% of the group actively treated with perindopril with or without indapamide compared with 11.0% of the placebo group (relative risk reduction of 19%; P=0.01).41 In contrast, 3 of the randomized trials reported no positive effects on cognitive function, motor skills, memory, or affect associated with antihypertensive therapy.35,38,42

There is also evidence to suggest that lowering BP may have a detrimental effect on cognitive function. Glynn et al and Bohannon et al independently demonstrated U-shaped relationships between BP levels and cognitive impairment on neuropsychological tests in cross-sectional and prospective longitudinal studies in 3657 and 1876 elderly individuals, respectively.43–44 In a longitudinal study of 56 elderly patients with symptomatic lacunar infarcts, Yamamoto et al found that cognitive performance declined in patients with reductions in BP levels at follow-up.45 Interestingly, the Rotterdam and Gothenburg H-70 studies of 6985 elderly individuals showed that the risk of cognitive impairment decreased with increasing BP (per 10 mm Hg systolic BP: relative risk=0.93; per
### TABLE 1. Cross-Sectional Studies Assessing the Effect of BP on Cognitive Function

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects Classification of Hypertension</th>
<th>Neurropsychological Test(s) Results/Conclusions</th>
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<tbody>
<tr>
<td>Wallace et al, 1985</td>
<td>2433 subjects; age ≥65; stroke-free</td>
<td>SBP ≥140 mm Hg (systolic hypertension); DBP ≥90 mm Hg (diastolic hypertension) Free-recall memory test</td>
</tr>
<tr>
<td>Farmer et al, 1987</td>
<td>2032 subjects; age 55–89; stroke-free</td>
<td>BP ≥160/95 mm Hg (hypertension); SBP ≥140 mm Hg and DBP &lt; 90 mm Hg (isolated systolic hypertension); DBP ≥90 mm Hg (diastolic hypertension) Logical memory-immediate recall, visual reproduction; paired associate learning, digits forward, digits backwards, word fluency, logical memory-delayed recall tests</td>
</tr>
<tr>
<td>Scherr et al, 1991</td>
<td>3809 subjects; age ≥65</td>
<td>SBP ≥140 mm Hg (systolic hypertension); DBP ≥90 mm Hg (diastolic hypertension) Immediate memory, delayed memory, mental status questionnaire, digit span tests</td>
</tr>
<tr>
<td>Starr et al, 1993</td>
<td>598 subjects; age ≥70; mean BP 160/86; no anti-hypertensive treatment</td>
<td>&gt;1 SD above mean BP (high BP); Within 1 SD of mean BP (medium BP); &gt;1 SD below mean BP (low BP) MMSE</td>
</tr>
<tr>
<td>Desmond et al, 1993</td>
<td>249 subjects; mean age 70.8; stroke-free</td>
<td>BP ≥160/95 mm Hg (hypertension) Selective reminding, Benton visual retention, similarities, verbal function, Rosen figure drawing, timed target-finding task tests</td>
</tr>
<tr>
<td>Kuuseisto et al, 1993</td>
<td>744 subjects; mean age 73; stroke-free; nondiabetic; mean BP of hypertensives 169/86 mm Hg; mean BP of normotensives 138/76 mm Hg</td>
<td>BP ≥160/95 mm Hg or on anti-hypertensive treatment MMSE, Russell adaptation of visual reproduction, trail making, verbal fluency, selective reminding tests</td>
</tr>
<tr>
<td>Gale et al, 1996</td>
<td>973 subjects; age ≥65</td>
<td>DBP ≥95 mm Hg (diastolic hypertension) Hodkinson abbreviated mental test</td>
</tr>
<tr>
<td>Guo et al, 1997</td>
<td>1736 subjects; age ≥75</td>
<td>SBP &lt;130 mm Hg (low SBP); SBP 130–150 (medium SBP); SBP 160–179 mm Hg (mildly elevated SBP); BP &gt;180/95 (severe hypertension) MMSE</td>
</tr>
<tr>
<td>Cacciatore et al, 1997</td>
<td>1106 subjects; age 65–95; stroke-free; mean BP 145/82 mm Hg</td>
<td>N/A MMSE</td>
</tr>
<tr>
<td>Van Boxtel et al, 1997</td>
<td>936 subjects; age 24–81; MMSE score &gt;24</td>
<td>BP ≥140/95 mm Hg (hypertension) Word learning task, concept shifting task, Stroop color word, letter/digit substitution, word fluency tests</td>
</tr>
<tr>
<td>Kilander et al, 1998</td>
<td>999 subjects; age 69–75; mean BP 149/85 mm Hg</td>
<td>N/A MMSE; trail-making test</td>
</tr>
<tr>
<td>Seux et al, 1998</td>
<td>2252 subjects; age ≥60; mean BP 173/86 mm Hg</td>
<td>SBP 160–219 mm Hg (systolic hypertension) MMSE</td>
</tr>
<tr>
<td>Izquierdo-Pomera et al, 2002</td>
<td>43 subjects; age 43–82; stroke-free; mean BP 136/78 MMSE ≥24</td>
<td>N/A Digits forward, digits backwards, word list learning, EXIT 25 executive functioning, clock drawing tests</td>
</tr>
<tr>
<td>Morris et al, 2002</td>
<td>5816 subjects; age ≥65</td>
<td>BP ≥160/90 mm Hg (hypertension) MMSE; East Boston memory, symbol digit modalities tests</td>
</tr>
<tr>
<td>Budge et al, 2002</td>
<td>158 subjects; age 60–91</td>
<td>N/A MMSE, Cambridge Examination for Mental Disorders of the Elderly—Cognitive Section</td>
</tr>
<tr>
<td>Pandav et al, 2003</td>
<td>4810 Indian subjects, age ≥55; mean BP 115/74; 636 North American subjects, age ≥75; mean BP 141/76</td>
<td>N/A MMSE, delayed recall tests</td>
</tr>
</tbody>
</table>
Many of the existing controversies on whether lowering BP under some circumstances, especially in older people, arises from the design limitations of older studies. Most studies did not quantify the level of cerebral SVD load in included subjects and did not consider this a relevant prognostic determinant. Although only patients with previous strokes were included in the PROGRESS Study, etiological subtyping was not undertaken. Reduction in cognitive decline was considered to be caused by reduction in number of large vessel infarcts and the effects of BP-lowering on SVD progression were not studied. Changes in cerebral autoregulation, which are known to affect cerebral perfusion, were not quantified, and the effects of BP reduction on structural vascular disease load were not assessed in these studies. Many studies used cognitive tests that have been shown to be insensitive to deficits characteristic of vascular cognitive impairment or allowed the use of beta-blocker or centrally acting anti-hypertensive agents, despite such drugs having the
potential to affect psychomotor performance. Furthermore, the results of the aforementioned studies are limited by the patient selection criteria and it is interesting to note that individuals with pre-existing cognitive dysfunction may have been excluded from many of the studies in view of difficulties with trial participation.

Emerging Concepts in Vascular Cognitive Impairment

It is generally accepted that hypertension accelerates arteriosclerotic changes in the brain and that early detection and antihypertensive therapy has a beneficial effect. Once established, chronic hypertension predisposes to atheroma formation in large-diameter blood vessels and arteriosclerosis and arteriolar tortuosity of small vessels (<400 μmol) of the cerebral vasculature. These small arteries and arterioles undergo medial thickening with hyaline deposition and intimal proliferation, which results in a reduction of luminal diameter and increased resistance to flow. As arterial narrowing increases, it leads to a decline in the perfusion of the capillary bed, which can result in ischemia and lacunar infarction. Chronic hypertension also predisposes to impaired blood brain barrier function, with endothelial cell retraction, increased vascular permeability, and greater susceptibility to white matter injury for relatively small insults. SVD of the brain not only increases cerebrovascular resistance but also is associated with impaired vasoconstrictor reactivity and decreased cerebrovascular dilatory capacity. This suggests that the effects of structural changes in the deep penetrating arteries may be compounded by functional limitations in adjusting CBF. Hence, systemic BP may become critical in maintaining adequate perfusion of deep subcortical structures (the natural watershed areas) in patients with established cerebrovascular disease. This is supported by studies that show that the limits of autoregulation are shifted upwards as a consequence of structural vascular adaptation in subjects with chronic hypertension and higher systemic BP is required to maintain adequate CBF.

The important question is whether BP-lowering to prevent further vascular events may have a deleterious effect on cerebral function in patients with cerebrovascular disease. Insight is provided by recent studies that have investigated correlations between day and night BP parameters and cerebrovascular disease. Karo et al demonstrated a J-shaped relationship between nocturnal BP decline, silent cerebrovascular damage, and stroke incidence in elderly asymptomatic hypertensive patients divided into nondippers, dippers, and extreme dippers, with the extent of cerebral vascular damage being most advanced in the extreme dipper group and least severe in the dipper group. A further study in elderly hypertensive patients showed a U-curve relationship between orthostatic BP change and silent cerebrovascular disease. In elderly hypertensive subjects, Kohara et al demonstrated a J-shaped relationship between nocturnal BP and the prevalence of lacunar infarction and showed postprandial hypotension to correlate with the extent of silent cerebrovascular disease. Prospective studies have also shown that nocturnal dipping is associated with increases in the severity of subcortical damage in patients with established cerebrovascular disease. These studies suggest that the threshold of BP needed to maintain CBF may shift to a higher level in elderly hypertensive individuals and that physiological episodes of low BP can provoke ischemic change in those with established cerebrovascular disease.

Conclusions

In conclusion, it is clear that BP reduction is beneficial in the majority of patients with vascular risk factors and will slow down the development of cerebrovascular disease, including SVD. That is not to say one should not be cautious about reducing BP in the elderly. The striking benefits achieved in the Syst-Eur and PROGRESS trials were achieved with very modest mean reductions in BP and one may consider avoiding the “sin of therapeutic greed” and settle for treatment targets in the elderly that may fall short of those recommended in recent guidelines. However, uncertainty surrounds the desirability of lowering of BP beyond a certain level in patients with established cerebral SVD. The extent to which BP should be lowered and whether there is a threshold beyond which BP reduction may have deleterious effects need to be determined. Refinement of criteria to select patients who will benefit from BP reduction and methods of assessment appear to be important and need further investigation. In patients with established cerebral SVD, risk-to-benefit ratio can only be assessed by randomized controlled trials including appropriate end-points that allow detection of cognitive consequences of subcortical ischemia, including executive dysfunction.

References


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*Stroke*. 2005;36:1308-1313; originally published online April 28, 2005;
doi: 10.1161/01.STR.0000165901.38039.5f

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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