In this issue of Hypertension, Odden et al¹ have reported on achieved blood pressures in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. After a mean follow-up of 3.7 (SD, 2.0) years, they found a J-shaped association between achieved blood pressure and outcomes, with the lowest risk at ≈124 mm Hg systolic and 67 mm Hg diastolic. The study randomized patients after a lacunar stroke to 2 systolic blood pressure (SBP) targets: <130 mm Hg or 130 to 149 mm Hg. Patients were also randomized to aspirin 325 mg alone or aspirin plus clopidogrel. In the intention-to-treat analysis² of the 2 blood pressure target groups, the only significant difference was a reduction of intracerebral hemorrhage with lower blood pressures. There was an excess of bleeding with dual antiplatelet therapy.

In this commentary, we address 2 key issues arising from this study: the J-shaped curve and poorer blood pressure control with a near doubling of stroke risk among black participants.

In this analysis of achieved blood pressures, both ischemic and hemorrhagic strokes declined with lower blood pressures down to 124/67 and then increased with further lowering of SBP. The authors suggest that lower blood pressure may increase the risk of both ischemic and hemorrhagic strokes. However, it is not biologically plausible that lower blood pressure would increase the risk of hemorrhagic stroke. Hypertensive intracerebral hemorrhage in the vascular centrencephalon—the basal ganglia, thalamus, brain stem, and cerebellum—is clearly caused by high perfusion. Average blood pressures conceal individuals with uncontrolled pressures. In the intent-to-treat analysis of SPS3, cardiovascular events were disproportionately more common among black patients in the higher pressure group (4.09% of black participants versus 2.23% of Hispanic and 2.56% of white participants). In this report, black participants were also more likely to have high achieved pressures despite more intensive therapy. In the Racial, Ethnic and Geographic Differences in Stroke (REGARDS) study, black participants were more likely to have uncontrolled blood pressure, although they were more likely to have hypertension diagnosed, more likely to have it treated, and more likely to have it treated more intensively. Stroke is twice as common in blacks as in other groups. This issue is important because it is remediable.

Among patients referred to a Canadian stroke prevention clinic, 50% had SBPs >140 mm Hg and 20% had diastolic blood pressures >90 mm Hg, and this did not change between 2002 and 2012. In contrast, levels of low-density lipoprotein cholesterol at the time of referral declined dramatically. Why is blood pressure harder to control than hypercholesterolemia? Patient causes of resistant hypertension include noncompliance, ingestion of substances that aggravate hypertension, such as salt, licorice, decongestants, and nonsteroidal anti-inflammatory agents (other than sulindac), and underlying causes of hypertension (secondary hypertension).
causes of uncontrolled hypertension include therapeutic inertia (reluctance to increase medication in the face of high office pressures) and diagnostic inertia (failure to investigate the underlying cause of resistant hypertension).

Therapeutic inertia may be because of preoccupation with a patient’s other medical problems, such as diabetes mellitus or arthritis, reluctance of the patient to take more medication, or a failure to understand that white coat hypertension is not benign. Therapeutic inertia can be overcome. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), site investigators were sent a letter insisting that the protocol be followed, whenever a patient attending a follow-up clinic had a blood pressure above the target and medication was not intensified. We reduced intracranial hemorrhage (including subarachnoid and lobar hemorrhage) to 0.4% of stroke.

However, diagnostic inertia seems more difficult to overcome. Although consensus guidelines recommend investigation of the cause when blood pressure is not controlled, this seldom happens; doctors continue to prescribe cookie-cutter therapy, as if all patients were the same. They are not, and this is particularly important for black patients. Black patients respond preferentially to diuretics, probably because of genetic causes of salt and water retention. It is well known that black patients have lower levels of plasma renin but seldom are the reasons considered appropriately. Blacks excrete a water load less well, thought to have a selective advantage for survival in hot climates. Blacks are more likely to have primary aldosteronism, probably due mainly to bilateral adrenocortical hyperplasia.

Liddle syndrome and variants, seldom considered, are much commoner than most physicians suppose. Mutations of the renal tubular epithelial sodium-channel cause salt and water retention, with excretion of potassium. The R563Q variant of Liddle syndromes was reported among hypertensives in 19.5% of Namibian San people, 18.8% of Northern Cape San, 9.1% of Nguni-Zulu, 6.4% of Sotho, and 6% of hypertensives in Cape Town. Another variant, T594M, was found in 5% of black hypertensives in London, United Kingdom, whereas in a Veterans’ Administration hypertension clinic in Louisiana, 6% of patients had a Liddle phenotype.

Why does this matter? Because the treatment of resistant hypertension is more effective if the right treatment is prescribed. Patients with primary aldosteronism, increasingly recognized as often being because of bilateral hyperplasia, should be treated with aldosterone antagonists (or surgery), and amiloride (a renal sodium-channel blocker) is the specific treatment for Liddle variants. These conditions are diagnosed by measuring plasma renin (preferably plasma renin activity) and aldosterone. Patients with low renin and high aldosterone levels have primary aldosteronism; those with low renin and low aldosterone levels have a Liddle variant or other cause of salt and water retention, whereas those with high renin and high aldosterone levels (secondary hyperaldosteronism) have hypertension that is being driven by renin and angiotsenin and will respond best to angiotensin receptor antagonists or renin inhibitors; they should also be investigated for renal causes of hypertension, such as obstruction, polycystic kidneys, a renal tumor, or renovascular hypertension.

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J. David Spence and Brian L. Rayner

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