

Intensive Blood Pressure Control Improves Cognitive Performance: Pushing the Envelope *cum Judicia*

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Hypertension is related to lower levels of cognitive performance and increased risk for mild cognitive impairment and dementia.¹ Cut points for hypertension have been revised downward over time, with current diagnostic criteria of $\geq 140/90$ mm Hg for hypertension and 120/80 to 139/89 mm Hg for prehypertension.¹⁻³ This trend is consistent with well-established findings that: (i) blood pressure (BP) is inversely associated with cognitive performance across the full range of normal and hypertensive BP levels¹⁻³ and; (ii) clinically notable reductions in cardiovascular events and death are observed following BP control to traditional ($<140/90$ mm Hg) and intensive ($<120/90$ mm Hg) targets.²⁻⁶

Due to significant improvement in physiological outcomes observed by the Systolic Blood Pressure Intervention Trial (SPRINT) research group,^{4,5} there is considerable interest in intensive management of BP to $<120/90$ mm Hg. In SPRINT, 9,361 treated and untreated hypertensive patients with systolic BP between 130 and 180 mm Hg, were randomized to receive standard (BP <140 mm Hg) or intensive treatment (<120 mm Hg). The main exclusions were diabetes mellitus, prior stroke, 1-minute standing BP <110 mm Hg, heart failure, polycystic kidney disease, and age <50 years. The trial was terminated after 3.3 years due to major benefits of intensive over standard treatment, including a 38% reduction in risk of heart failure, a 43% reduction in risk of death from cardiovascular causes, and a 27% reduction in risk of death from any cause.⁵ Given that cardiovascular disease moderates and modifies associations between blood pressure and cognitive function, one would expect to see parallel benefits to cognitive functioning.

In this issue of the *American Journal of Hypertension*, Lamar *et al.*⁷ report that intensive treatment of hypertension is associated with improved cognitive function. Importantly, the Lamar *et al.* study deals specifically with Hispanic and Latino adults living in the United States, a population lagging behind other ethnic groups by 10 to 15 percent with respect

to BP control using standard criteria. It seems likely that findings from this study will generalize to other populations, albeit empirical confirmation of this assumption is necessary.

The primary sample consisted of treated hypertensive individuals between 44 and 74 years of age ($N = 1735$) with verified antihypertensive medication histories. Three automated blood pressure measurements were obtained with an OMRON HEM-907 XL automatic sphygmomanometer after a 5-minute rest period. The conventional target of BP control ($<140/90$ mm Hg) was achieved in 63% of the participants and intensive control ($<120/90$ mm Hg) in 23%.

Multiple regression analyses were used to relate BP control status to each measure of cognitive functioning utilized (Table 1). Analyses were adjusted for age and various demographic, cardiovascular, and immigration-related variables. Participants achieving traditional BP control exhibited greater verbal fluency with adjustment for age and better information processing speed with full adjustment compared to those who were uncontrolled.

Achievement of intensive BP control was associated with better verbal fluency performance regardless of statistical adjustments. Direct comparison of control criteria revealed that participants with intensive BP control had significantly better verbal fluency performance than those with traditional BP control regardless of adjustment, albeit this relationship was only observed in women after sex stratification. Sensitivity analyses including hypertensive participants who were untreated and those with unverified medication histories yielded similar findings for many associations. Number of classes of medications used to achieve treatment targets was not associated with cognitive functioning.

A strength of the study was that patients with a history of psychotropic medication use were excluded from all analyses. This is important given reported interactions between psychotropic and hypertensive medications, which are often disregarded in studies of cognition and BP.⁸

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Initially submitted February 22, 2017; accepted for publication March 1, 2017; online publication April 11, 2017.

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doi:10.1093/ajh/hpx043

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Table 1. Associations between BP control and performance on each cognitive measure utilized with adjustment for demographic, cardiovascular, and immigration-related variables

Domain indexed	Cognitive measure	Range of scores	Improvement in scores ^a		
			Traditional vs. uncontrolled	Intensive vs. uncontrolled	Intensive vs. traditional
Verbal fluency	Number of words beginning with a specified letter generated in 60 seconds	0–50	N.S.	1.64 (0.54) ^b	1.41 (0.58)
Information processing speed	Digit Symbol Substitution Test	0–80	1.43 (0.59)	N.S.	N.S.
Learning	Brief Spanish English Verbal Learning Test: learning trials	0–45	N.S.	N.S.	N.S.
Memory	Brief Spanish English Verbal Learning Test: free recall	0–15	N.S.	N.S.	N.S.

Abbreviation: N.S., nonsignificant.

^aResults reported are raw regression coefficients (with standard errors) obtained using model 2: treatment-related control status + age + sex + background + education + Six-Item Screener score + Center for Epidemiologic Studies Depression Scale score + current smoking status + presence of diabetes + presence of hypercholesterolemia + health insurance status + income + immigrant generational status + language-based acculturation.

^bRemained significant in sensitivity analyses including untreated hypertensives and those with unverified medication histories; a direct comparison of BP criteria was not performed.

Table 1 shows raw regression coefficients with the possible range of scores on each cognitive outcome. The improvement in cognitive performance with intensive management of BP was modest, with only a few points gained on each measure. This is true for many studies with traditional BP targets.¹ Lamar *et al.* note the limited clinical significance of the findings, but propose that small improvements could have population-level significance. We agree; even small improvements in cognitive performance have major implications for treatment-related risk reduction at a population level. Seventy-five million adults in the United States have hypertension, many of which have characteristics similar to those in the SPRINT study.⁹ Thus, we may expect that intensive BP control would decrease population risk for lowered cognitive performance.

However, health care providers treat individuals, not populations.¹⁰ Here, the question is whether modest gains justify the risk of intensive treatment goals. Oparil and Lewis¹¹ remind us that “the large benefits of intensive treatment in SPRINT come at some cost.” While there were no statistically significant differences in adverse events between conventional and intense treatment in SPRINT, adverse events such as orthostatic hypotension and falls leading to injury, hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure were more frequent in the intensive group as compared to the standard treatment group (4.7 and 2.5%, p 1308). This is a small differences in adverse events, albeit the population attributable risk issue applies here as well as it does to cognitive benefits. Small amounts of risk make a difference in large populations of individuals. But, forewarned is forearmed and SPRINT alerts us to which adverse effects are likely to be seen following similar protocols.

Findings by Lamar *et al.*⁷ encourage pushing the envelope of risk vs. benefit because their protocol was similar to the SPRINT protocol in important features (e.g., automated BP measurement), suggesting that improved cognition may be a collateral benefit to lowered cardiovascular events in carefully conducted trials. However, until there are further trials,

the decision to treat intensively lies with the health care provider. This decision must be informed and take into account the specifics of SPRINT as they apply to subject selection (nondiabetics free from prior stroke, adults 50 years or older, persons free from prior stroke). Moreover, health care providers who wish to employ intensive treatment strategies would benefit by having full appreciation for individual differences in cognitive ability,¹² variability of cognitive performance levels around the BP-cognition regression line¹³ and individual and racial/ethnic variability in positive response to treatment.^{14,15} There have been few studies of these variables in relation to successful response to treatment. More are needed.

While the use of automated BP measurement in SPRINT has been criticized as not reflecting office practice in measurement of BP, it is our hope that SPRINT and the Lamar *et al.* studies will encourage a movement toward accurate measurement of BP, an essential element in patient safety. Strongly supported by the literature,¹⁵ Oparil and Lewis¹¹ argue that BP measurement in the office is often flawed. It is common practice for BP measurements to be taken manually with a sphygmomanometer, with little or no rest period prior to measurement, improper cuff size and placement, feet not flat on the floor, etc. These flawed procedures may result in overestimation of BP and consequent overtreatment of hypertension. Automated office BP measurement, as in SPRINT and in Lamar *et al.*, is essential to avoid treating BP to dangerously low levels based on spuriously high BP values. One must avoid rise in BP associated with the alerting response to doctors and nurses (white coat rise in BP); patients should be instructed in systematic home BP measurement (with devices calibrated to the office device). Hopefully, research may tell us to what extent nocturnal monitoring of dipping and nondipping is a necessary adjunct to intensive BP treatment, albeit this is an expensive adjunct to safety monitoring.

The Lamar *et al.* study has identified important clinical issues with respect to intensive treatment to improve

cognition, especially since negative findings have been reported in some trials, even with conventional BP lowering.^{1,16} Replication of the study in other ethnic populations and with more comprehensive cognitive test batteries is needed.¹ Obviously longitudinal studies are absolutely critical, as we must determine if improved cognition in mid-life protects against mild-cognitive impairment and conversion to dementia later in life. Verdecchia *et al.*⁶ go to the heart of these issues with respect to pushing the envelope for better cognition: “At the end of 2016, the stage seems set for lower BP targets to reduce the risk for stroke and heart attack (we add cognitive deficit), but *cum judicium*.”

DISCLOSURE

The authors declared no conflict of interest.

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