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Commentary

Goal blood pressure for cognition–impaired patients: let's treat the patients—not the numbers

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Mossello et al[1] recently published an observational study of demented or cognitively impaired patients recruited from outpatient memory clinics in Italy. They recorded day– and night–time blood pressure (BP) using ambulatory BP monitors in addition to office BP determinations. Their outcome measure was change in the Mini–Mental State Examination (MMSE) score from baseline to follow–up (median duration, 9 months). They observed that patients with dementia or mild cognitive impairment that were treated with antihypertensive medications and whose BP was in the lowest systolic tertile (<128 mm Hg) had a significant decrease in MMSE scores (ie, declining cognitive performance) compared with the second (systolic blood pressure [SBP], 129–144 mm Hg) and third tertiles (SBP ≥145 mm Hg). This was true only for the patients who were being treated with antihypertensive medications and not for unmedicated people. They opined that excessive SBP lowering may be harmful for older patients with cognitive impairment.

In the same issue of JAMA Internal Medicine, Sabayan and Westendorp[2] reviewed and commented on studies of the relationship of SBP to cognitive function and provided an excellent review of the physiologic effects of elevated SBP (and reduction to low values in some cases) on cerebral vascular function, including sufficient nourishment of brain cells. In their words, "The link between blood pressure and cognitive impairment is a complex beast." Both papers take issue with the "lower the better" concept, and both call for well–designed interventional studies in the high–risk aged. An answer to this question may come from the Systolic Blood Pressure Intervention Trial (SPRINT) trial of an aggressive BP target of <120 mm Hg versus <140 mm Hg, with a substantial proportion of elderly participants followed by cognitive testing and expert adjudication of cognitive outcomes. But the expected completion date is late 2018.

Our purpose here is to make a few points that we believe to be clinically relevant. First, there is evidence that elevated BP (>140/>90 mm Hg) in mid–life is associated with an increased risk of executive and cognitive dysfunction and dementia in later life.[3] We believe that our goal should be focused on prevention of cerebral dysfunction by treating elevated BP early on and certainly by mid–life. Even prehypertension carries an increased risk of stroke.[4,5] Given the near complete lack of evidence, it is difficult to advocate for treatment of patients with the higher end of prehypertension (SBP, 130–139 mm Hg; diastolic blood pressure [DBP], 85–89 mm Hg) even though Trial of Preventing Hypertension (TROPHY) showed prevention of progression to stage 1 hypertension by treatment with an angiotensin receptor blocker (ARB) compared with placebo.[6] In addition, there appeared to be a legacy effect in which the SBP of treated subjects did not rise to the level of the placebo–treated group by 4 years even when the active drug was stopped (blindly) at 2 years. Animal models suggest a vascular healing effect if animals are treated when young.[7] There are no current guidelines for the pharmacologic treatment of prehypertension, and one could make valid arguments against such treatment due to cost and the large numbers needed to treat this group of individuals. Nevertheless, a naturally occurring SBP as low as 115 mm Hg seems to convey significant protection against stroke compared with higher numbers.[8] At the very least, we should pay attention to treating stage 1 and higher BP in an effort to prevent target organ damage, especially for the most sensitive target organ: the brain. But, the long–term cognitive consequences of such treatment are of interest and as of yet unknown.

Second, we have to wonder about treating the "frail" or cognitively impaired elderly with antihypertensive medications to such low BP as in the bottom tertile group reported by Mossello et al.[1] What is the purpose? Demented people do not suddenly become normal as soon as their SBP is

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reduced. If that were so, there would be no need for studies of this topic. It is a joy for us to see people in their 80s and 90s who are remarkably functional even if they suffer some of the physical infirmities associated with aging. Our clinical judgment is that if SBP is elevated in this age group, it should be treated with caution to about 150 mm Hg if the treatment is well–tolerated.[9] And, if they are already well–controlled on antihypertensive medication when they cross the threshold of 80 years, they should continue ''as is,'' as long as they feel well. Such decisions are relegated to providers at all levels who are supposed to possess and use similar ''clinical judgment.'' So, Mosello and his colleagues have done us the favor of saying clearly: do not treat elderly cognitively impaired patients to arbitrary low BP goals, but further randomized data are clearly needed.

Third, we would be more than a little distressed were the Mosello paper misinterpreted to prevent the treatment of non–frail elderly people who have hypertension. As late as the 1980s, the prevailing wisdom was that drug treatment of hypertension in the elderly could reduce their functional IQ, activities of daily living, and motor skills, and adversely affect their mood.[10] Two studies from the VA Cooperative Study Group on Antihypertensive Agents challenged that ''wisdom.''[11,12]

They studied 690 hypertensive but otherwise healthy men over 60 years of age (mean, 64.3 $\pm$ 4.1 years; 12.1% were $\geq$70 years with the oldest being 88 years old). They were first randomly allocated to treatment with either low dose (25–50 mg) or high dose (50–100 mg) hydrochlorothiazide (HCTZ). If patients failed to achieve goal BP on the 50 or 100 mg dose, they were randomly allocated to treatment with hydralazine (25, 50, or 100 mg twice daily), methyldopa (250, 500, or 1000 mg twice daily), metoprolol (50, 100, or 200 mg twice daily), or reserpine (0.05, 0.10, or 0.25 mg once daily). The study was double–blinded using a double–dummy drug packaging method because identical appearing placebos were not available for the four second–tier drugs. Significant findings included a 58.2% response to diuretic titration, 92.8% of whom completed a 6–month maintenance period, response to the previously untested 25 mg dose of HCTZ, and the relative good tolerance to the second tier drugs, three of which are infrequently used today. It was also clear that a second drug added to HCTZ had a significant additional BP–lowering effect.

A second phase of the study was designed to determine whether BP reduction, per se, causes adverse effects on cognitive and behavioral function in elderly hypertensive patients. During the placebo and maintenance period (up to 1 year), patients had their cognitive function, motor skills, memory, and affect tested by a battery of psychometric tests. A subset of patients received placebo to control for practice effects. There were no differences between the lower and higher dose diuretic groups, and no differences between the second level drugs. In fact, all improved so that there was indeed a practice effect. Therefore, reduction of BP and use of drugs then thought to be potentially detrimental actually did not have a negative effect. They concluded that BP reduction, per se, did not adversely affect cognitive and behavioral function in this elderly cohort and that antihypertensive treatment was safe and effective in these patients.

Even using drugs such as reserpine, they demonstrated not only that there was no impairment of any of these factors, but that the scores went up. As demonstrated by a control group that also increased scores, this was largely a learning effect, but the point was that there was no decline—and that these elderly subjects were able to learn. Low adverse–effect drugs that are available today leave little or no excuse for failing to treat patients to the older BP targets used in that study.

One thing we do not know is how the patients' with BP levels in the lowest tertile got into that category or why they were cognitively impaired. Both of these are potentially important factors. Some may simply have been continued on their medications unnecessarily. In a memory clinic sample, Alzheimer's disease (AD; the most common single entity) may lead to low blood pressure due to autonomic system damage, and clinicians should be vigilant about polypharmacy. Others with AD may also have active hypertension and could have been treated to BP levels in the lowest tertile, but whether that is good or bad probably depends on patient–specific factors. In those without concomitant cerebrovascular damage, further cognitive decline could be incidental and not caused by the lower BPs. However, vascular contributions are now understood to be even more common in those with cognitive impairment than either pure AD or vascular dementia. As any clinician knows, it is quite common to see so-called ''silent'' or ''subclinical infarcts'' on brain imaging. In those with a history of stroke, or subclinical lesions in locations that cause cognitive impairment, treating hypertension may be an effective way of preventing further small vessel damage, but to what level requires further randomized trials.

As nicely reviewed in one of the editorial citations,[13] the cognitive impairment itself may in part be related to dysfunctional cerebral autoregulation. Normally, the brain's resistance vessels maintain constant perfusion across a wide range of BP values, even down to a mean BP of 60 mm Hg. However, chronic hypertension leads to arterial stiffness that damages resistance vessels and shifts this autoregulatory curve to the right, making the brain susceptible at BP levels normally above ischemic thresholds, perhaps even at values corresponding to some in the lowest tertile

of the Mosello et al study. Thus, one subgroup in the Mosello study could have included hypertensives with impaired autoregulation wherein treatment to such low levels contributed to their cognitive decline. White matter lesions commonly seen on neuroimaging are a risk factor for dementia,[14] are often a consequence of cerebral small vessel disease, and occur in border zone areas between territories of penetrating arterioles that are susceptible to hypoperfusion. Further data are needed to understand the relationship between aggressive BP treatment, impaired autoregulation, and their cognitive sequelae, another question poised to be answered by SPRINT.

In summary, cognitively impaired people should not be subjected to aggressive antihypertensive treatment that is unlikely to be of benefit. We should do all that we can to prevent cognitive dysfunction by treating hypertension earlier in life and appropriately. We should not be dissuaded from treating people who need, and who will likely benefit from, treatment based on these results in cognitively impaired patients, but more data are needed to define the subgroups who may or may not benefit.

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