ECRONICON OPEN ACCESS

EC CARDIOLOGY
Commentary

May a Stricter Blood Pressure Control Stop or Delay the Progression of Mild Cognitive Impairment to Dementia in Patients with Hypertension?

Antonio Coca* and Cristina Sierra

Hypertension and Vascular Risk Unit, Department of Internal Medicine, Hospital Clínic (IDIBAPS), University of Barcelona, Spain

***Corresponding Author:** Antonio Coca, Hypertension and Vascular Risk Unit, Department of Internal Medicine, Hospital Clínic (IDIBAPS), University of Barcelona, Spain.

Received: March 19, 2019; **Published:** April 22, 2019

The benefits of blood pressure (BP) reduction on the incidence of stroke, coronary artery disease, heart failure and chronic kidney disease are well known, and the recent 2018 ESC/ESH Hypertension Guidelines [1] recommends achieving BP targets < 130/80 mmHg in the majority of patients for primary prevention of stroke, if treatment is well tolerated. This recommendation is similar to the 2017 ACC/AHA Guidelines [2].

Hypertension in middle age has been associated with cognitive decline and dementia in the elderly. In fact, hypertension induces long-term structural changes in the deep penetrating small cerebral arteries, and endothelial dysfunction, leading to a silent ischemic process in these vessels, which may be detected as white matter lesions (WML), silent lacunar infarcts (SLI) and microbleeds (MBs) by magnetic resonance image (MRI). The pathophysiology of brain damage induced by high BP is represented in figure 1. All these lesions evolve for years in a silent manner until the final clinical event in the form of hemorrhagic or ischemic stroke. In addition, there is robust evidence supporting that silent small vessels cerebral disease is also associated with cognitive decline and dementia. More than fifteen years ago we showed that this process starts in the middle age in untreated hypertensive patients [3]. Since then many studies has confirmed the relationship between high BP, structural silent brain lesions and cognitive decline [4].

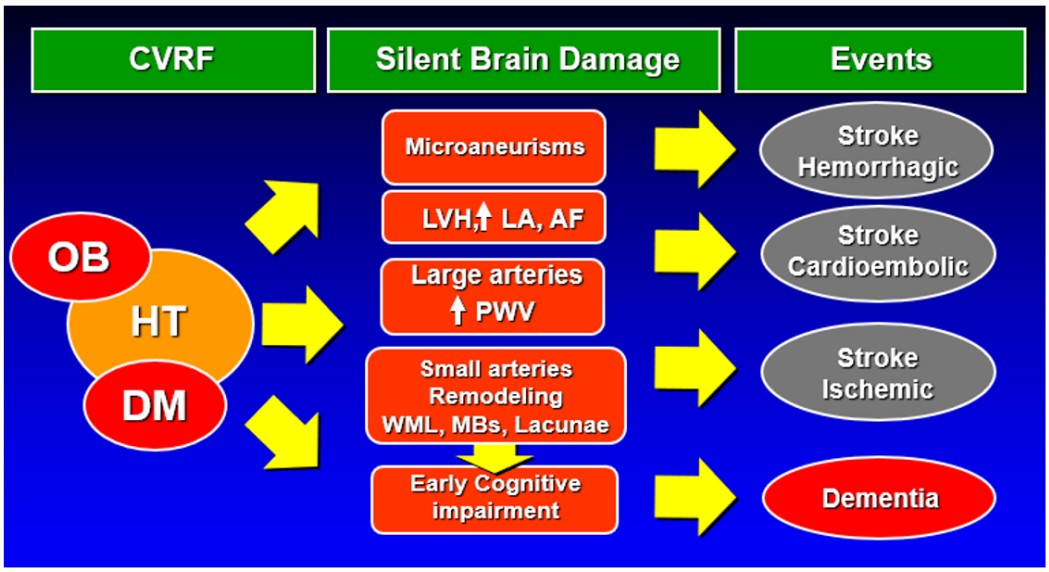

Figure 1: *Pathophysiology of brain damage in hypertension. CVRF: Cardiovascular Risk Factors; OB: Obesity; HT: Hypertension; DM: Type 2 Diabetes Mellitus; LVH: Left Ventricular Hypertrophy; LA: Left Atrium; AF: Atrial Fibrillation; PWV: Pulse Wave Velocity; WML: White Matter Lesions; MBs: Microbleeds.*

Due to the relationship between high BP and cognitive dysfunction it could be hypothesized that reduction of BP by antihypertensive treatment may stop, or at least delay, the progression from mild cognitive impairment to vascular dementia and Alzheimer's disease. In other words, strict and sustained BP control in middle age of life could prevent dementia in the elderly [5]. In this sense, some clinical trials of prevention on morbidity and mortality in patients with hypertension such as the Syst-Eur trial [6] and the PROGRESS trial [7] and a meta-analysis of 14 studies in which the incidence of dementia during treatment was included as a secondary endpoint, have shown that antihypertensive treatment may reduce the incidence of vascular dementia and Alzheimer's disease in elderly patients, as well as that no specific drug or strategy is better than other preventing cognitive decline [8].

However, the majority of data concerning the effect of antihypertensive drugs on cognitive decline and dementia come from observational studies or registries, in which the lack of randomization and inclusion bias impede to obtain solid conclusions. On the other hand, several studies have shown that sustained BP control during 4 to 5 years reduced new onset WML in comparison with untreated or uncontrolled hypertensive patients [9]. For this reason the recent 2018 ESC/ESH Hypertension Guidelines [1] maintain a pragmatic view concerning the antihypertensive strategy in prevention of silent brain damage, recommending the combination of a drug blocking the renin-angiotensin system (Angiotensin Converting Enzyme inhibitor or Angiotensin-II Receptor Blocker) with a calcium channel blocker or a thiazide (thiazide-like) diuretic, preferably in a single pill to improve adherence and long-term persistence on treatment.

Even considering the hypothesis that BP control may reduce the incidence of cognitive decline and its evolution to dementia in patients with hypertension, the optimal BP target had not been explored until the SPRINT MIND study [10]. This is a substudy of the SPRINT designed to evaluate the incidence of probable dementia (primary endpoint), and the incidence of mild cognitive impairment (MCI) and the combination of probable dementia and MCI as secondary endpoints, in relation to intensive treatment strategy (systolic BP goal < 120 mmHg) in comparison with standard treatment strategy (systolic BP goal < 140 mmHg). Among 9361 randomized patients with hypertension aged 50 years or older (mean age 67.9 years; 35.6% women) 8563 (4278 patients in the intensive arm and 4285 in the standard arm) were included for the final analysis. None of them had diabetes or a history of stroke as were the criteria for inclusion in SPRINT study. Cognitive status screening was performed at baseline and at least after one year of follow-up and included a test of global cognitive function (Montreal Cognitive Assessment [MoCA]; range, 0 - 30), learning and memory (Logical Memory forms I and II subtests of the Wechsler Memory Scale; ranges, 0 - 28 and 0 - 14), and processing speed (Digit Symbol Coding Test of the Wechsler Adult Intelligence Scale; range, 0 - 135). Mean duration of treatment was 3.34 years.

The incidence of dementia was 149 patients in the intensive treatment and 176 patients in the standard treatment group, with a 17% non-significant reduction in the intensive group (hazard ratio [HR] 0.83; 95% CI, 0.67 - 1.04). However, a significant 19% reduction of mild cognitive impairment was observed in the intensive treatment group (HR 0.81; IC 95% 0.69 - 0.95), and a significant 15% reduction of the combined secondary endpoint of MCI and probable dementia (HR 0.85; IC 95% 0.74 - 0.97) compared with the standard group (Table 1). These results were similar for all pre-specified subgroups (by age < 75 or ≥ 75 tears, sex, black vs. nonblack race, history of cardiovascular disease, chronic kidney disease, tertiles of SBP ≤ 132; 132 - 145; ≥ 145 mmHg, and presence or absence of orthostatic hypotension). The lack of a significant reduction of the primary outcome in the intensive group was probably related with the small number of cases of incidental dementia during a relative short follow-up for this hard outcome. On the contrary, MCI was much more frequent outcome with 287 cases in the intensive group and 353 cases in the standard group, having enough statistical power to prove the study hypothesis.

Events (Intensive vs. standard)	HR	95% CI	% RR (p)
Incidence of mild cognitive impairment (MCI)	0.81	0.70 - 0.95	19% (p = 0.01)
Incidence of probable dementia (Dem)	0.83	0.67 - 1.04	17% (p = 0.10)
Combined incidence of MCI + Dem	0.85	0.74 - 0.97	15% (p = 0.02)
WML volume increase during 4 years (cm^3)			
Intensive treatment	0.28		(p = 0.04)
Standard treatment	0.92		

Table 1: *Effect of intensive systolic blood pressure reduction (< 130 mmHg) vs. standard reduction (< 140 mmHg) in the incidence of dementia or mild cognitive impairment in a subgroup of 8563 participants in the SPRINT MIND study.*

In summary, SPRINT MIND is the first randomized clinical trial demonstrating that lowering systolic BP below 130 mmHg (is important to note that average SBP in the intensive group was 121.6 mmHg) significantly reduces the progression of mild cognitive impairment compared with less intensive BP lowering (average SBP was 134.8 mmHg in the standard group) in patients with hypertension. Perhaps a more prolonged follow-up of study patients could be accompanied by a higher number of dementia events, then having enough statistical power to show also a significant reduction of incidental dementia. Anyway, SPRINT MIND strengthens the recommendations of the most recent American and European Hypertension Guidelines [1,2] of achieving in most patients with hypertension, independently of their total cardiovascular risk, a BP goal lower than 130/80 mmHg in primary prevention of cardiovascular events and cognitive decline, provided that treatment is well tolerated. Antihypertensive drug treatment should start as soon as possible in middle aged patients with the aim of preventing cognitive impairment and dementia in the elderly.

Bibliography

1. Williams B., *et al*. "2018 ESC/ESH Guidelines for the management of arterial hypertension". *Journal of Hypertension* 36.10 (2018): 1953-2041.

2. Whelton PK., *et al*. "2017 ACC /AHA /AAPA/ABC /ACPM/AGS / APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines". *Journal of the American College of Cardiology* 71.6 (2018): 2176-2198.

3. Sierra C., *et al*. "Silent cerebral white matter lesions in middle-aged essential hypertensive patients". *Journal of Hypertension* 20.3 (2002): 519-524.

4. Sierra C., *et al*. "Hypertension, Cognitive Decline, and Dementia". In: Coca A (Ed.). Hypertension and Brain Damage. Updates in Hypertension and Cardiovascular Protection. Switzerland, Springer, Cham (2016): 197-211.

5. Coca A. "Hypertension and vascular dementia in the elderly: the potential role of anti-hypertensive agents". *Current Medical Research and Opinion* 29.9 (2013): 1045-1054.

6. Forette F., *et al*. "Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study". *Archives of Internal Medicine* 162.18 (2002): 2046-2052.

7. The PROGRESS Collaborative Group. "Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease". *Archives of Internal Medicine* 163.9 (2003): 1069-1075.

8. Levi N., *et al*. "Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis". *Journal of Hypertension* 31.6 (2013): 1073-1082.

9. Verhaaren BF., *et al*. "High blood pressure and cerebral white matter lesion progression in the general population". *Hypertension* 61.6 (2013): 1354-1359.

10. The SPRINT MIND Investigators for the SPRINT Research Group. "Effect of Intensive vs. Standard Blood Pressure Control on Probable Dementia. A Randomized Clinical Trial". *Journal of the American Medical Association* 321.6 (2019): 553-561.

Volume 6 Issue 5 May 2019
©All rights reserved by Antonio Coca and Cristina Sierra.