Effects of Low Blood Pressure in Cognitively Impaired Elderly Patients Treated With Antihypertensive Drugs

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**IMPORTANCE** The prognostic role of high blood pressure and the aggressiveness of blood pressure lowering in dementia are not well characterized.

**OBJECTIVE** To assess whether office blood pressure, ambulatory blood pressure monitoring, or the use of antihypertensive drugs (AHDs) predict the progression of cognitive decline in patients with overt dementia and mild cognitive impairment (MCI).

**DESIGN, SETTING, AND PARTICIPANTS** Cohort study between June 1, 2009, and December 31, 2012, with a median 9-month follow-up of patients with dementia and MCI in 2 outpatient memory clinics.

**MAIN OUTCOMES AND MEASURES** Cognitive decline, defined as a Mini-Mental State Examination (MMSE) score change between baseline and follow-up.

**RESULTS** We analyzed 172 patients, with a mean (SD) age of 79 (5) years and a mean (SD) MMSE score of 22.1 (4.4). Among them, 68.0% had dementia, 32.0% had MCI, and 69.8% were being treated with AHDs. Patients in the lowest tertile of daytime systolic blood pressure (SBP) (<128 mm Hg) showed a greater MMSE score change (mean [SD], −2.8 [3.8]) compared with patients in the intermediate tertile (129-144 mm Hg) (mean [SD], −0.7 [2.5]; P = .002) and patients in the highest tertile (>145 mm Hg) (mean [SD], −0.7 [3.7]; P = .003). The association was significant in the dementia and MCI subgroups only among patients treated with AHDs. In a multivariable model that included age, baseline MMSE score, and vascular comorbidity score, the interaction term between low daytime SBP tertile and AHD treatment was independently associated with a greater cognitive decline in both subgroups. The association between office SBP and MMSE score change was weaker. Other ambulatory blood pressure monitoring variables were not associated with MMSE score change.

**CONCLUSIONS AND RELEVANCE** Low daytime SBP was independently associated with a greater progression of cognitive decline in older patients with dementia and MCI among those treated with AHDs. Excessive SBP lowering may be harmful for older patients with cognitive impairment. Ambulatory blood pressure monitoring can be useful to help avoid high blood pressure overtreatment in this population.
High blood pressure (HBP) and various forms of cognitive impairment are highly prevalent and frequently associated with old age. According to recent data, 54% of older men and 57% of older women have HBP. Dementia affects 6% to 8% of persons 60 years or older and up to 25% of persons 85 years or older. Mild Cognitive Impairment (MCI), a less severe form of cognitive decline that may herald the development of overt dementia, is observed in a large proportion of individuals 65 years or older, with prevalence estimates of approximately 25%. It has been shown that dementia is the main cause of incident disability in the elderly and that Alzheimer disease is the sixth leading cause of death among Americans of white race/ethnicity.

The association between HBP and dementia is controversial. Results of cross-sectional investigations on an association between blood pressure and cognitive function are contradictory. Several prospective studies with long-term follow-up have found a higher risk of dementia, including Alzheimer disease, in patients with HBP. Other longitudinal studies, especially those that include participants 75 years or older, have demonstrated that higher blood pressure is associated with lower incidence of dementia.

Evidence on the prognostic role of HBP in individuals with cognitive impairment is even more limited and inconsistent, especially for overt dementia. A recent study of persons with MCI showed that higher blood pressure is associated with more rapid cognitive decline. In agreement with these data, observational studies have shown a protective effect of the use of antihypertensive drugs (AHDs) on cognitive function of older individuals with dementia or MCI. On the other hand, onset of overt dementia is typically associated with spontaneous lowering of blood pressure, with a potential risk of overtreatment if drug therapy is not adequately modified. Moreover, no rigorous intervention studies to date have been specifically performed among older persons with cognitive impairment, and large randomized trials on the treatment of HBP in the elderly failed to resolve this controversy. It has been hypothesized that, owing to brain hypoperfusion, hypotension may adversely affect cognitive outcome in dementia, although no experimental evidence exists of altered cerebral blood flow autoregulation in patients with Alzheimer disease.

There is a lack of solid evidence to guide the treatment of HBP in older persons with dementia and MCI. The most recent guidelines from the European Society of Hypertension and the European Society of Cardiology leave decisions on antihypertensive therapy of elderly patients with frailty to the treating physician and do not provide treatment targets for patients with cognitive impairment. No specific recommendation for the oldest old, frail, and cognitively impaired elderly has been given by the American 2014 Eighth Joint National Committee guidelines.

Ambulatory blood pressure monitoring (ABPM) may provide additional prognostic information over usual office blood pressure measurement in predicting mortality and major adverse cardiovascular events (MACEs). Moreover, agreement between office and monitored blood pressures is poor in institutionalized persons with cognitive impairment, particularly owing to the high prevalence of white-coat hypertension. To our knowledge, no longitudinal study has been conducted in older individuals with cognitive impairment using ABPM to predict changes in their cognitive status. Therefore, we studied the association of blood pressure (using both office and ABPM data) and AHD treatment with mental status changes in older persons with cognitive impairment.

Among a group of older individuals with dementia or MCI, the primary objective of this observational cohort study was to evaluate the role of office blood pressure, 24-hour ABPM, and AHD prescription in predicting a decrease in cognitive function and the progression of disability. As a secondary outcome, we examined the effect of office and ABPM values on adverse events, including deaths, MACEs, hospitalizations, syncope, falls, and fractures.

Methods

Study Design
The study was approved by the ethics committee of Azienda Ospedaliero Universitaria Careggi, Florence, Italy. Each individual gave written informed consent to participate in the study. Each study participant completed a baseline assessment (T0) and a follow-up assessment after 6 to 18 months (T1).

We enrolled individuals referred to 2 outpatient memory clinics from June 1, 2009, to May 31, 2011, and from September 1, 2012, to December 31, 2012. These clinics included the Division of Geriatric Cardiology and Medicine, Department of Medicine and Geriatrics, Azienda Ospedaliero Universitaria Careggi, Florence, and the Azienda Unità Sanitaria Locale 3, Pistoia, Italy.

Inclusion criteria for the study were age 65 years or older, a diagnosis of dementia (according to Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition] criteria) or MCI (according to the International Working Group on Mild Cognitive Impairment consensus criteria), and a Mini-Mental State Examination (MMSE) score of 10 to 27 (score range of 0-30, with 0 indicating maximum cognitive impairment). Exclusion criteria were permanent atrial fibrillation, owing to limited accuracy of automated blood pressure measurement in this condition, or refusal to wear the ABPM device or to participate in follow-up assessments. For patients with moderate to severe cognitive impairment, special attention was given to explain the aims and procedures of the study, with involvement of a family caregiver if needed in the consenting process.

Recorded at T0 were 5 data elements. First were main vascular comorbidities, including HBP, diabetes mellitus, chronic heart failure, coronary heart disease, cardiac arrhythmias other than permanent atrial fibrillation, cerebrovascular disorder, and chronic kidney disease. Each of these conditions was diagnosed based on clinical history, medical records, and physical examination and was scored as present (1 point) or absent (0 points), summing to a vascular comorbidity score ranging from 0 to 7. Second was ongoing treatment with any AHD. These included angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, β-blockers, angiotensin II type 1 receptor antagonists, and α-adrenergic blocking agents. Third was measurement of office systolic blood pressure (SBP) and
diastolic blood pressure (DBP). A mercury sphygmomanometer was used in accord with international guidelines.\textsuperscript{19} Fourth was a cognitive assessment, which was based on the MMSE score.\textsuperscript{25} Fifth was disability in basic activities of daily living (BADL) and instrumental activities of daily living (IADL).\textsuperscript{27,28} The scores ranged from 0 to 6 for BADL and from 0 to 8 for IADL, with higher scores indicating more severe disability.

At T0, all participants underwent ABPM using an oscillometric method (model 90207; Spacelabs Healthcare). The ABPM was offered to all participants irrespective of HBP diagnosis. The pressure measurement cuff was applied to the nondominant arm. Cuffs of adequate size were applied, choosing between 3 to cover at least 80% of the arm circumference. The device was set to automatically detect blood pressure every 15 minutes (with a warning sound) during the daytime (7:00 AM to 10:00 PM) and every 20 minutes (without sound) during the nighttime (10:00 PM to 7:00 AM). In the case of a failed measurement, a second one was automatically performed within 2 minutes. According to their cognitive level, participants were instructed verbally about the functioning of the device and on the necessity to keep their arm steady and relaxed during the measurements. A first measurement was performed in the clinic after application of the device to verify its correct functioning and participant compliance.

Three ABPM variables were calculated. First were the mean ambulatory 24-hour daytime (9:00 AM to 9:00 PM) and nighttime (1:00 AM to 6:00 AM) SBPs and DBPs. Daytime and nighttime values were calculated with the fixed narrow interval approach, excluding rising and retiring periods, in accord with European guidelines on blood pressure monitoring.\textsuperscript{29} Second was blood pressure variability, which was defined by the SDs of SBPs. Third was nighttime blood pressure dipping, which was measured as the difference between the mean daytime and nighttime SBPs and expressed as the percentage of daytime SBP.

At T1, office blood pressure, MMSE score, BADL, and IADL were again measured. Based on patient and caregiver report and available health records, we also recorded deaths, MACEs, hospitalizations, syncope, falls, and fractures in the entire study population. To reduce loss to follow-up at T1 owing to adverse events, participants were contacted by telephone.

**Statistical Analysis**

Office blood pressure and ABPM variables were categorized into tertiles. Continuous variables (reported as means and SDs) and categorical variables (reported as percentages) were compared at T0 across tertiles of clinical and ABPM blood pressures. No imputation was performed for missing data.

The progression of cognitive decline and disability was calculated as the differences in MMSE, BADL, and IADL scores between T1 and T0. The differences were compared across tertiles of each blood pressure variable. The same analysis was repeated after stratification by the use of AHDs. A multivariable comparison was performed, adjusting for age, baseline MMSE score, vascular comorbidity score, AHD treatment, and the interaction between blood pressure variables and AHD treatment. The same analyses were conducted in the whole sample and in the dementia and MCI subgroups.

Between-group comparisons were performed using analysis of variance (with Bonferroni correction for post hoc analysis) for continuous variables or using Kruskal-Wallis test for nonnormally distributed variables. Comparison of categorical variables was performed with Pearson $\chi^2$ test. Pre-post comparisons were performed with paired $t$ test for continuous variables or with Wilcoxon signed rank test for nonnormally distributed variables.

Multivariable analysis was performed with analysis of covariance, introducing categorical variables as fixed factors and continuous variables as covariates. Estimated marginal means (with 95% CIs) resulting from the models were calculated. Analyses were performed with statistical software (SPSS, version 20; IBM). $P < .05$ was considered statistically significant.
who were treated with AHDs. The mean (SD) MMSE score changes were −3.9 (3.5) in the lower tertile vs −0.6 (2.2) in the intermediate tertile and −0.4 (3.7) in the highest tertile (<0.001 for both) (Figure 2A). A similar trend for association, although weaker, was found for office SBP. Participants in the lowest tertile showed a greater cognitive decline if treated with AHDs (mean [SD], −2.7 [3.7] for the lowest tertile vs −0.9 [3.6] for the highest tertile; *P* = .06) and a better cognitive outcome if untreated (mean [SD], 1.3 [2.8] for the lowest tertile vs −1.8 [3.1] for the highest tertile; *P* = .01) (Figure 2B). Similar results were found for nighttime SBP. Participants in the lowest tertile (mean, ≤119 mm Hg) showed a trend for a worse cognitive outcome if treated with AHDs compared with the highest tertile (>135 mm Hg), with mean (SD) MMSE score changes of −2.2 (3.7) for the lowest tertile vs −1.0 (4.0) for the highest tertile (*P* = .45). However, the difference between groups was not statistically significant.

The multivariable model in Figure 3 included age, baseline MMSE score, vascular comorbidity score, SBP tertile, and AHD treatment. The interaction term between low SBP and...
AHD treatment was independently associated with a greater cognitive decline for daytime SBP ($F = 6.139, P = .003$) and for office SBP ($F = 7.393, P = .001$). The mean (95% CI) adjusted MMSE score change by daytime SBP among patients who were taking AHD were $-3.9$ ($-4.9$ to $-2.8$) for the lowest tertile, $-0.7$ ($-1.7$ to $0.4$) for the intermediate tertile, and $-0.4$ ($-1.4$ to $0.6$) for the highest tertile. The same values for nontreated patients were $-0.4$ ($-2.1$ to $1.3$) for the lowest tertile, $-0.8$ ($-2.3$ to $0.7$) for the intermediate tertile, and $-1.4$ ($-3.1$ to $0.3$) for the highest tertile. The mean (95% CI) adjusted MMSE score change by office SBP among patients who were taking AHD were $-2.7$ ($-3.8$ to $-1.7$) for the lowest tertile, $-1.2$ ($-2.3$ to $-0.1$) for the intermediate tertile, and $-0.9$ ($-2.0$ to $0.2$) for the highest tertile. The same values for nontreated patients were $1.4$ ($-0.4$ to $3.3$) for the lowest tertile, $-1.3$ ($-3.1$ to $0.6$) for the intermediate tertile, and $-1.8$ ($-3.2$ to $-0.4$) for the highest tertile (Figure 3).

Subgroup Analysis
The same statistical analysis was performed within the dementia and MCI subgroups. Patients with dementia in the lowest tertile of daytime SBP showed a greater MMSE score decline (mean [SD], $-3.5$ [4.1]) compared with patients in the intermediate tertile (mean [SD], $-0.6$ [2.8]; $P = .004$) and patients in the highest tertile (mean [SD], $-1.2$ [4.1]; $P = .003$). Similarly, patients with MCI in the lowest tertile of daytime SBP showed a greater cognitive decline (mean [SD], $-1.4$ [2.7]) compared with patients in the highest tertile (mean [SD], $0.8$ [1.9]; $P = .02$). No association between MMSE score change and office SBP was observed in the dementia subgroup or the MCI subgroup.

Again, an association between low daytime SBP and a greater cognitive decline was observed only among patients who were taking AHDs in the dementia subgroup and in the MCI subgroup. Multivariable analysis performed within subgroups (Figure 4) confirmed an independent association between a greater cognitive decline and the interaction term between low daytime SBP and AHD treatment in the dementia subgroup ($F = 3.592, P = .03$) and in the MCI subgroup ($F = 4.907, P = .01$). In the dementia subgroup, the mean (95% CI) adjusted MMSE score change by daytime SBP among patients who were taking AHD were $-4.4$ ($-5.8$ to $-3.1$) for the lowest tertile, $-1.0$ ($-2.4$ to $0.5$) for the intermediate tertile, and $-0.6$ ($-2.0$ to $0.7$) for the highest tertile. The same values for

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**Figure 2. MMSE Score Change by AHD Treatment and Daytime and Office SBPs**

<table>
<thead>
<tr>
<th>SBP Range</th>
<th>Treated With AHDs</th>
<th>Not Treated With AHDs</th>
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</thead>
<tbody>
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<td>$\leq 128$ mm Hg</td>
<td>$P &lt; .001$</td>
<td>$P = .06$</td>
</tr>
<tr>
<td>$129-144$ mm Hg</td>
<td>$P &lt; .001$</td>
<td>$P = .01$</td>
</tr>
<tr>
<td>$\geq 145$ mm Hg</td>
<td>$P = .06$</td>
<td>$P = .01$</td>
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</table>

**Figure 3. MMSE Score Change by AHD Treatment and Daytime and Office SBPs**

AHD indicates antihypertensive drug; MMSE, Mini-Mental State Examination; and SBPs, systolic blood pressures.
nontreated patients were $-0.7 (-3.3$ to $1.8$) for the lowest tertile, $-0.3 (-2.4$ to $1.8$) for the intermediate tertile, and $-2.0 (-4.3$ to $0.2$) for the highest tertile. In the MCI subgroup, the mean (95% CI) adjusted MMSE score change by daytime SBP among patients who were taking AHD was $-2.9 (-4.1$ to $-1.7$) for the lowest tertile, $-0.4 (-1.7$ to $0.8$) for the intermediate tertile, and $0.4 (-0.8$ to $1.6$) for the highest tertile. The same values for nontreated patients were $0.4 (-1.2$ to $2.1$) for the lowest tertile, $-1.3 (-3.1$ to $0.6$) for the intermediate tertile, and $0.7 (-1.5$ to $2.8$) for the highest tertile (Figure 4). The same analysis performed for office SBP confirmed an independent association in the dementia subgroup but not in the MCI subgroup.

**Adverse Clinical Events**

Among 177 participants, 3 (1.7%) died, 17 (9.6%) experienced a MACE, 12 (6.8%) had a bone fracture, 47 (26.6%) reported at least 1 fall, 12 (6.8%) reported an episode of syncope, and 42 (23.7%) were hospitalized during the follow-up period. No significant between-group difference in these events was observed across tertiles of office SBPs and daytime SBPs, although a nonsignificant trend for higher incidences of syncope and hospitalization was observed with decreasing daytime SBPs. In the lowest, intermediate, and highest tertiles of daytime SBPs, syncope incidence rates were 10.5%, 6.8%, and 3.4%, respectively ($P = .33$), and hospitalization rates were 33.3%, 21.7%, and 17.2%, respectively ($P = .11$).

**Discussion**

In the present sample of cognitively impaired older adults, low daytime SBPs measured with ABPM were associated with a greater progression of cognitive decline after a median 9-month follow-up. This association was limited to patients treated with AHDs and was independent of age, vascular comorbidity score, and baseline cognitive level; it remained significant in the dementia subgroup and in the MCI subgroup. A similar trend for association was observed for office SBP, although this trend was weaker and did not reach statistical significance in all analyses. Lower blood pressure was not associated with better health-related outcomes.

The prognostic role of blood pressure on the progression of dementia is uncertain. In Alzheimer disease, one study showed no association between blood pressure and cognitive outcome, another study observed a negative prognostic effect of higher blood pressure on cognitive outcome only at younger ages, while a third study found a similar association only in those 85 years or older. Conversely, in the Leiden...
85-plus Study\textsuperscript{25} enrolling individuals 85 years or older (with cognitive impairment in 65\% of participants), cognitive decline after 3 years was milder in those with higher SBPs, especially in the presence of severe disability at baseline.

The findings of the Leiden 85-plus Study\textsuperscript{11} are consistent with results of the present study, which found an association between lower SBP and poorer cognitive outcome in older patients with dementia and MCI after a short follow-up period. Because lower blood pressure has been associated with brain atrophy in old age,\textsuperscript{33} low SBP may be a marker of a more severe neurodegenerative process. However, no correlation between cognitive function and blood pressure was observed herein at T0, while the longitudinal association remained significant after adjustment for baseline MMSE score. Despite the small sample size, the association was significant in the subgroup with MCI, in whom neurodegeneration was presumably mild or absent.

Two studies have focused on the prognostic effect of vascular risk factors, including HBP, in individuals with MCI and observed an association with higher risk of dementia\textsuperscript{34} and cognitive decline.\textsuperscript{33} However, in those studies, the follow-up duration was longer (5 years\textsuperscript{15} and 2 years\textsuperscript{13}) and the mean age younger (66 years\textsuperscript{15} and 74 years\textsuperscript{13}) compared with the present study. Moreover, in the present study, the association between low SBP and cognitive decline, in agreement with previous research,\textsuperscript{40} was observed only in individuals treated with AHDs, while the opposite trend was observed in the untreated individuals, supporting the hypothesis of a negative cognitive effect of strict blood pressure control. Although the use of AHDs may be a marker of coexistent cardiac diseases, such as heart failure, associated with reduced cognitive performance,\textsuperscript{34} the association remained significant after adjustment for vascular comorbidity.

A notable feature of the present study is the use of ABPM, suggesting that low daytime SBP is more accurate than clinical measurement in detecting an association between low SBP and a greater cognitive decline. In particular, daytime ABPM (and not office SBP measurement) was associated with cognitive outcome in the entire sample of treated and untreated individuals and in the final model relating to the MCI subgroup. Owing to its greater simplicity, office blood pressure measurement should be the first step, although we advise routine use of ABPM before starting or upgrading antihypertensive treatment in this frail population if office SBP is elevated. Conversely, nighttime SBP and DBP, blood pressure dipping, and blood pressure variability showed no statistically significant association with cognitive outcome. To our knowledge, 24-hour blood pressure variables have not been studied before as prognostic predictors in individuals with cognitive impairment. Cross-sectional investigations of ABPM and cognition in a general elderly population found inconsistent results, with various studies showing that lower cognitive function was associated with nondipping,\textsuperscript{35-37} higher 24-hour DBP,\textsuperscript{38} lower daytime and nighttime SBP,\textsuperscript{38} higher blood pressure variability,\textsuperscript{39} or no ABPM variable.\textsuperscript{40}

Primary limitations of the present study include the small sample size and its observational design, which prevent us from drawing definite conclusions regarding the detrimental effect of AHDs on cognitive status. Other limitations were the short follow-up period, which does not allow us to detect possible long-term protective effects of such treatment, and the setting of an outpatient memory clinic, which does not allow direct generalization of results to primary or acute care. Moreover, owing to the lack of constant availability of staff and ABPM equipment, not all of the potential candidates were enrolled, although the absence of specific exclusion criteria other than the stated ones makes the presence of a selection bias unlikely.

Despite these limitations, we believe that the present data add useful information in regard to the treatment of HBP in cognitively impaired older adults. In the randomized clinical Hypertension in the Very Elderly Trial,\textsuperscript{41} which showed the efficacy of antihypertensive treatment in the prevention of MACE and death in participants 80 years or older, adults with an SBP of 160 mm Hg or higher and without severe comorbidity (including dementia) were enrolled. No specific treatment recommendation exists for older adults with HBP and cognitive impairment or dementia.\textsuperscript{19,20} A previous study\textsuperscript{23} of elderly nursing home residents (a population often affected by dementia) demonstrated no prognostic effect of blood pressure, with a poor correlation between office and ABPM values. Those data raised doubts regarding the clinical meaning of office blood pressure in cognitively impaired older adults.

Conclusions
The present study adds information about older outpatients with MCI and dementia, suggesting that strict control of SBP may negatively affect cognition, with daytime SBPs of 130 to 145 mm Hg being the most appropriate therapeutic targets. Longitudinal ABPM studies of larger samples with longer follow-up periods are needed to fully evaluate the long-term prognostic effects of blood pressure in older adults with cognitive impairment. Randomized clinical trials would be able to assess the risks and benefits of antihypertensive treatment with different targets in this population.

**ARTICLE INFORMATION**

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REFERENCES


