ORIGINAL RESEARCH

Blood Pressure Lowering With Nilvadipine in Patients With Mild-to-Moderate Alzheimer Disease Does Not Increase the Prevalence of Orthostatic Hypotension

Rianne A. A. de Heus, MSc; Rogier Donders, PhD; Angelina M. M. Santoso, MSc; Marcel G. M. Olde Rikkert, MD, PhD; Brian A. Lawlor, MD; Jurgen A. H. R. Claassen, MD, PhD; for the Nilvad Study Group*

***Background*—**Hypertension is common among patients with Alzheimer disease. Because this group has been excluded from hypertension trials, evidence regarding safety of treatment is lacking. This secondary analysis of a randomized controlled trial assessed whether antihypertensive treatment increases the prevalence of orthostatic hypotension (OH) in patients with Alzheimer disease.

***Methods and Results*—**Four hundred seventy-seven patients with mild-to-moderate Alzheimer disease were randomized to the calcium-channel blocker nilvadipine 8 mg/day or placebo for 78 weeks. Presence of OH (blood pressure drop ≥20/≥10 mm Hg after 1 minute of standing) and OH-related adverse events (dizziness, syncope, falls, and fractures) was determined at 7 follow-up visits. Mean age of the study population was 72.2±8.2 years and mean Mini-Mental State Examination score was 20.4±3.8. Baseline blood pressure was 137.8±14.0/77.0±8.6 mm Hg. Grade I hypertension was present in 53.4% (n=255). After 13 weeks, blood pressure had fallen by −7.8/−3.9 mm Hg for nilvadipine and by −0.4/−0.8 mm Hg for placebo (P<0.001). Across the 78-week intervention period, there was no difference between groups in the proportion of patients with OH at a study visit (odds ratio [95% CI]=1.1 [0.8–1.5], P=0.62), nor in the proportion of visits where a patient met criteria for OH, corrected for number of visits (7.7±13.8% versus 7.3±11.6%). OH-related adverse events were not more often reported in the intervention group compared with placebo. Results were similar for those with baseline hypertension.

***Conclusions*—**This study suggests that initiation of a low dose of antihypertensive treatment does not significantly increase the risk of OH in patients with mild-to-moderate Alzheimer disease.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT02017340. **(*J Am Heart Assoc*. 2019;8: e011938. DOI: 10.1161/JAHA.119.011938)**

Key Words: adverse drug event • Alzheimer disease • antihypertensive agent • calcium channel blocker • orthostatic hypotension • randomized controlled trial

With an estimated prevalence of 45%, hypertension is a common comorbidity among patients with Alzheimer disease (AD).[1] Despite this high prevalence, this patient group has not been represented in hypertension trials, leading to uncertainty regarding the benefit-to-risk ratio of antihypertensive treatment in these patients.[2] This same discussion concerns frail, older people in general.[3] In the absence of evidence, current guidelines advise being cautious when starting antihypertensive treatment in these groups.[4–6]

From the Department of Geriatric Medicine, Radboud University Medical Center, Donders Institute for Brain Cognition and Behaviour, Nijmegen, The Netherlands (R.A.A.d.H., A.M.M.S., M.G.M.O.R., J.A.H.R.C.); Radboudumc Alzheimer Center, Nijmegen, The Netherlands (R.A.A.d.H., A.M.M.S., M.G.M.O.R., J.A.H.R.C.); Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands (R.D.); Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland (B.A.L.); Department of Medical Gerontology, Trinity College Institute of Neuroscience, Dublin, Ireland (B.A.L.).

Accompanying Tables S1 through S5 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.011938

*A complete list of the Nilvad Study Group is provided in the Appendix at the end of the article.

Correspondence to: Jurgen Claassen, MD, PhD, Department of Geriatric Medicine, Radboud University Medical Center, P.O. Box 9101, 6500 HB, Internal postal code 925, Nijmegen, The Netherlands. E-mail: jurgen.claassen@radboudumc.nl

Received January 28, 2019; accepted April 16, 2019.

Clinical Perspective

What Is New?

- Lowering blood pressure with a low dose of the calcium-channel blocker nilvadipine does not increase the prevalence of orthostatic hypotension in patients with mild-to-moderate Alzheimer disease.
- This finding was independent of initial blood pressure level or frailty score.

What Are the Clinical Implications?

- This study adds to the discussion on the benefit-to-risk ratio of antihypertensive treatment in patients with Alzheimer disease.

A widely voiced concern among physicians is that older people develop orthostatic hypotension (OH) following antihypertensive treatment.[7] The prevalence of OH increases with age,[8] and has been associated with cognitive decline,[9] possibly caused by AD pathology. OH is an independent risk factor for future falls.[10] Therefore, if antihypertensive treatment increases the risk of OH, it could unintentionally lead to increased frailty, institutionalization, or mortality,[11] especially in AD, where cerebral hypoperfusion following OH could accelerate cognitive decline.[12]

Evidence about antihypertensive treatment and OH has mainly emanated from observational studies,[13–16] while results from randomized clinical trials in healthy older people showed that improved control of blood pressure (BP) did not result in a larger difference between sitting and standing BP.[17,18] Whether this also holds for frail populations, such as patients with AD, is currently unknown.

The Nilvad trial was designed to investigate the putative anti-amyloid properties of the calcium-channel blocker nilvadipine in mild-to-moderate AD.[19] The trial result was negative for cognitive and functional outcomes.[20] However, nilvadipine's antihypertensive properties are comparable to other, more commonly used, calcium-channel blockers.[21,22] Therefore, preplanned monitoring of BP throughout the study allowed us to explore the effect of starting an antihypertensive drug on the prevalence of OH in AD. Specifically, the aim of this study was to investigate whether BP lowering with nilvadipine increased the prevalence of OH and OH-related clinical outcomes in patients with mild-to-moderate AD.

Methods

Because of agreements within the Nilvad consortium, the data that support the findings of this cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure. The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Study Design

The Nilvad trial (NCT02017340) was a randomized, double-blind, placebo-controlled trial, conducted at 23 sites in 9 European countries. The trial was approved by institutional review boards of each participating country, and all patients as well as relevant caregivers gave written informed consent. A complete description of the trial has been published previously.[19] The main outcome of the trial and any changes made to the study protocol after trial commencement have been reported by Lawlor et al (2018).[20]

Participants

Patients were recruited from 13 academic and 10 general memory clinics. Patients were eligible if they (1) met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association[23] for the diagnosis mild-to-moderate probable AD, (2) were aged ≥50 years, (3) scored between 12 and 26 on the Mini-Mental State Examination,[24] (4) had a caregiver available, and (5) were not using a calcium-channel blocker, β-blocker, or α-blocker. For safety reasons, since the trial was not designed to investigate BP lowering, BP had to be between 100 and 159 mm Hg for systolic and between 65 and 99 mm Hg for diastolic BP. Patients using a cholinesterase inhibitor or memantine were eligible if they were on a stable dose for 3 months before screening. The main exclusion criteria were dementia resulting from other causes and the presence of a medical condition that, according to the physician, would preclude participation. A detailed list of inclusion and exclusion criteria is provided in the trial protocol.[19]

Intervention

The trial used a parallel-group design with a 1:1 allocation ratio to 8 mg nilvadipine or placebo once daily. Antihypertensive properties of 8 mg of nilvadipine are comparable to 5 mg of amlodipine.[22] Randomization and blinding processes have been described elsewhere.[19] Briefly, randomization was stratified by study site and all study staff was blind to randomization. Study medication was dispensed per 98 capsules at baseline and at every 13-week follow-up. Compliance was monitored by collecting the used treatment packs and leftover capsules at each visit. Postrandomization visits occurred at weeks 6, 13, 26, 39, 52, 65, and 78.

Measurements

At every visit, intermittent BP was measured by qualified study site staff after 5 minutes of rest in the sitting position, and again after 1 and 5 minutes of standing, using a manual sphygmomanometer. Any symptoms noted during standing were recorded. At baseline, the Alzheimer's Disease Assessment scale[25] was used to assess cognitive function, the Disability Assessment for Dementia questionnaire[26] was used to assess functional abilities, and the Clinical Dementia Rating scale[27] was used to characterize dementia stage. For patients who had consented to the Nilvad frailty-substudy, a baseline frailty index was derived.[28,29] This index comprised the ratio of deficits present out of 26 possible deficits across multiple domains, resulting in a score between 0 and 1 (see Table S1 for a detailed description). We classified patients as fit (index ≤0.10), less fit (0.10<index≤0.21), or frail (index>0.21) analogous with the SPRINT (Systolic Blood Pressure Intervention Trial) criteria.[30] Adverse events and concomitant medication use were assessed using structured interviews with patient and caregiver at every visit. Concomitant medication was coded according to the Anatomical Therapeutic Chemical classification system. The study allowed initiation or termination of other antihypertensive medication in case patients developed high or low BP during the study.

Outcomes

We constructed 3 dichotomous outcomes of OH. Classic OH: a drop of ≥20 mm Hg in systolic blood pressure (SBP) or ≥10 mm Hg in diastolic blood pressure (DBP) after 1 minute of standing compared with sitting BP (consensus criteria);[31] sit-to-stand OH: a drop of ≥15 mm Hg in SBP or ≥7 mm Hg in DBP after 1 minute of standing;[32] and symptomatic OH: the presence of symptoms upon standing, irrespective of the drop in BP. This latter category (symptoms suggestive of OH) was included to reduce the risk of missing OH because of false-negative intermittent BP measurements. In addition, we examined the change in SBP from sitting to standing on a continuous scale (ΔSBP, in mm Hg and %) and the presence of classic OH after 5 minutes of standing, referred to as delayed OH.[13] Clinical outcomes were reported adverse events of fractures, falls, syncope, and dizziness.

Statistical Analyses

The effect of treatment on OH was examined in 2 ways. First, multivariable logistic regression examined the effect of treatment on the proportion of OH at follow-up, with fixed effects for treatment, baseline ΔSBP (mean-centered), time and time*treatment interaction, and random intercepts for patient and study center, to address correlations resulting from repeated measures and center-specific effects. In case time*treatment interaction was not significant, it was dropped from the model. Second, we examined the effect of treatment on the number of follow-up visits in which a patient met criteria for OH, using the total number of visits for that patient as the denominator. Descriptive summaries of these results are presented.

In addition, linear regression was applied to examine the effect of treatment on ΔSBP, with fixed effects for treatment, baseline ΔSBP, time and time*treatment interaction, and random intercepts for patient and study center. The effect of treatment on the presence of reported clinical outcomes during follow-up was evaluated with logistic regression.

To test for any potential moderating effects, the following baseline variables and the interaction term for these variables with treatment were added as predictors in the analyses described above: BP status (high: ≥140/90 mm Hg, normal: 130 to 139/70 to 89 mm Hg or low: <130/70 mm Hg BP at baseline), Mini-Mental State Examination score, age, frailty index, diabetes mellitus, use of additional antihypertensive medication parallel to the intervention, use of cholinesterase inhibitors, and use of antidepressants.

Analyses were performed on the per protocol population, including only measurements of patients with ≥80% treatment compliance in the 3-month window before that particular measurement. A complete cases analysis (patients included in all 7 follow-up visits) was performed as well. Missing values were not imputed. Two-sided testing and an alpha level of 0.05 were used. Since the analyses were performed post hoc, *P* values should be interpreted with caution and 95% CI of the outcomes that are reported were appropriate. Analyses were performed with SPSS Statistics software version 22.0 and R.[33]

Results

Characteristics

The Nilvad trial was conducted between May 2013 and November 2016. Among 511 randomized patients, 477 (93.3%) were included in the current per protocol analysis (Figure 1). The proportion of patients who completed all 7 follow-up visits was 68.3% for nilvadipine and 70.5% for placebo (*P*=0.61). Table 1 shows the baseline demographics and clinical characteristics. Characteristics were the same for the complete cases (Table S2). Reasons to be excluded from the per protocol analysis are detailed in Table S3. The proportion of patients who continuously used an antihypertensive agent parallel to the intervention was 25.4% for nilvadipine and 31.6% for placebo (*P*=0.13). In the nilvadipine group, 5.0% started with an additional antihypertensive drug, whereas 7.9% stopped one. In the placebo group this was 9.3% versus 6.8%, respectively.

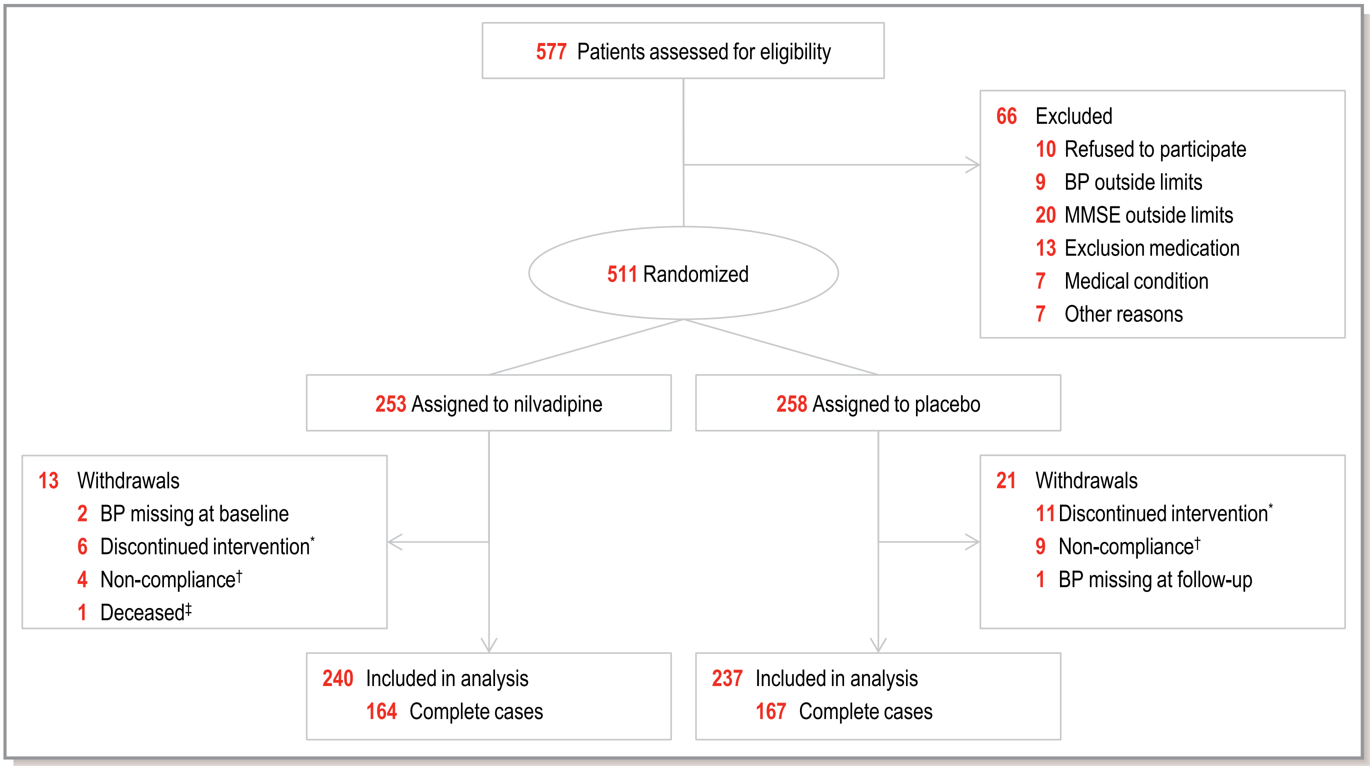


Figure 1. Flow of participants. *Patients who discontinued the intervention before attending the first follow-up visit at week 6. †Patients who were not compliant with the study medication (compliance <80%) during any of the 3-month windows preceding a follow-up visit. ‡One patient deceased before the first follow-up visit at week 6 occurred. BP indicates blood pressure; MMSE, Mini-Mental State Examination score.

Changes in Sitting Blood Pressure

Figure 2 shows the mean sitting SBP and DBP throughout the study. At baseline, sitting SBP and DBP were 138.3±13.7 mm Hg (mean±SD) and 76.7±8.7 mm Hg for nilvadipine and 137.2±14.2 mm Hg and 77.2±8.6 mm Hg for placebo. The proportion of patients with baseline hypertension (BP≥140/90 mm Hg) was 57.1% for nilvadipine and 49.8% for placebo. After 13 weeks of treatment, sitting SBP and DBP had dropped by 7.8±14.0 and 3.9±8.7 mm Hg for nilvadipine and with 0.4±14.1 and 0.8±9.1 mm Hg for placebo (P<0.001 for SBP and DBP). This effect did not differ between those with high, normal, and low BP at baseline (Figure S1), nor between those who did, versus did not, use additional antihypertensive drugs parallel to the intervention (Figure S2). Similar results were observed for the complete cases (Figure S2).

Orthostatic Hypotension and Clinical Outcomes

Of 477 patients, 32.9% (n=79) in the nilvadipine group and 34.6% (n=82) in the placebo group met the criteria for classic OH at least once during follow-up. These proportions were 52.7% and 47.3% for sit-stand OH, 8.3% and 11.4% for symptomatic OH, and 38.3% and 32.9% for delayed OH, in the nilvadipine and placebo group, respectively. None of the OH outcomes had a significant time*treatment interaction (classic OH: P=0.47, sit-stand OH: P=0.78, symptomatic OH: P=0.23, delayed OH: P=0.52), and therefore this term was dropped from the models.

Across the 78-week follow-up, there was no statistically significant difference between nilvadipine and placebo in the proportion of patients at a study visit meeting the criteria for classic OH (odds ratio [OR]=1.1 [0.8–1.5], P=0.62), sit-stand OH (OR=1.2 [0.9–1.5], P=0.15), symptomatic OH (OR=0.8 [0.3–2.3], P=0.55), or delayed OH (OR=1.2 [0.9–1.6], P=0.26) (Figure 3). In addition, there was no clinically relevant effect of nilvadipine on ΔSBP upon standing (in mm Hg: β=−0.8 [−1.7 to 0.2], P=0.13, in %: β=−0.6 [−1.3 to 0.2], P=0.12, see Figure 4). Similar results were observed for complete cases (Table S4).

The proportion of visits where a patient met criteria for OH did not differ between the groups. For nilvadipine and placebo, respectively, these proportions were: 7.7±13.8% and 7.3±11.6% for classic OH, 14.8±18.7% and 12.2±15.5% for sit-stand OH, 1.8±6.6% and 2.4±8.0% for symptomatic OH, and 8.5±14.3% and 7.3±12.3% for delayed OH.

There were no differences between the groups in the prevalence of OH-related relevant clinical outcomes of fractures, falls, syncope, or dizziness (Figure 5).

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Placebo (n=237)	Nilvadipine (n=240)
Women, no. (%)	138 (58.2)	156 (65.0)
Age, mean (SD), y	72.0 (7.9)	72.4 (8.6)
Aged ≥75 y, no. (%)	93 (39.2)	112 (46.7)
Time since diagnosis of AD, median (IQR), y	0.9 (0.4–2.3)	1.3 (0.5–2.4)
Mini-Mental State Examination score, mean (SD)	20.5 (3.9)	20.3 (3.8)
AD Assessment Scale—cognitive subscale, mean (SD)	34.6 (10.8)	34.5 (10.5)
Clinical Dementia Rating—sum of boxes, mean (SD)	5.2 (2.7)	5.4 (2.8)
Frailty index, median (IQR)*	0.17 (0.10–0.27)	0.18 (0.11–0.26)
Fit (index≤ 0.10), no. (%)	56 (25.6)	49 (22.3)
Less fit (0.10<index≤0.21), no. (%)	90 (41.1)	86 (39.1)
Frail (index>0.21), no. (%)	73 (33.3)	85 (38.6)
Body mass index, mean (SD), kg/m^2	25.9 (4.4)	25.3 (4.0)
Sitting systolic blood pressure, mean (SD), mm Hg	137.2 (14.2)	138.3 (13.7)
Sitting diastolic blood pressure, mean (SD), mm Hg	77.2 (8.6)	76.7 (8.7)
High blood pressure, no. (%)	118 (49.8)	137 (57.1)
Normal blood pressure, no. (%)	93 (39.2)	76 (31.7)
Low blood pressure, no. (%)	26 (11.0)	27 (11.3)
Resting heart rate, mean (SD), beats per min	70.1 (10.3)	70.7 (10.3)
Classic orthostatic hypotension, no. (%)	22 (9.3)	17 (7.1)
Sit-to-stand orthostatic hypotension, no. (%)	33 (13.9)	38 (15.8)
Symptomatic orthostatic hypotension, no. (%)	3 (1.3)	10 (4.2)
Delayed orthostatic hypotension, no. (%)	20 (8.4)	14 (5.8)
Δ Systolic blood pressure, mean (SD), mm Hg	−0.3 (10.2)	−1.8 (9.6)
Δ Systolic blood pressure, mean (SD), %	0.0 (7.3)	−1.1 (7.0)
Use of medication at study enrollment, no. (%):		
At least 1 antihypertensive medication	90 (38.0)	80 (33.3)
≥2 antihypertensive medications	11 (4.6)	8 (3.3)
Angiotensin II receptor blocker	40 (16.9)	33 (13.8)
Angiotensin-converting-enzyme inhibitor	46 (19.4)	38 (15.8)
Diuretic	13 (5.5)	18 (7.5)
Cholinesterase inhibitors	212 (89.5)	210 (87.5)
Memantine	62 (26.2)	64 (26.7)
Antidepressants	83 (35.0)	89 (37.1)
Benzodiazepines	12 (5.1)	7 (2.9)
Antipsychotics	11 (4.6)	11 (4.6)
Statins	79 (33.3)	84 (35.0)
Antithrombotics	58 (24.5)	61 (25.4)
History of cardiovascular disease, no. (%)	19 (8.0)	19 (7.9)
Diabetes mellitus, no. (%)	8 (3.4)	28 (11.7)

High blood pressure: ≥140/90 mm Hg; normal blood pressure: 130 to 139/70 to 89 mm Hg; low blood pressure: <130/70 mm Hg. AD indicates Alzheimer disease; IQR, interquartile range; no., number.
*n=219 placebo, n=220 nilvadipine (consented to Nilvad frailty-substudy).

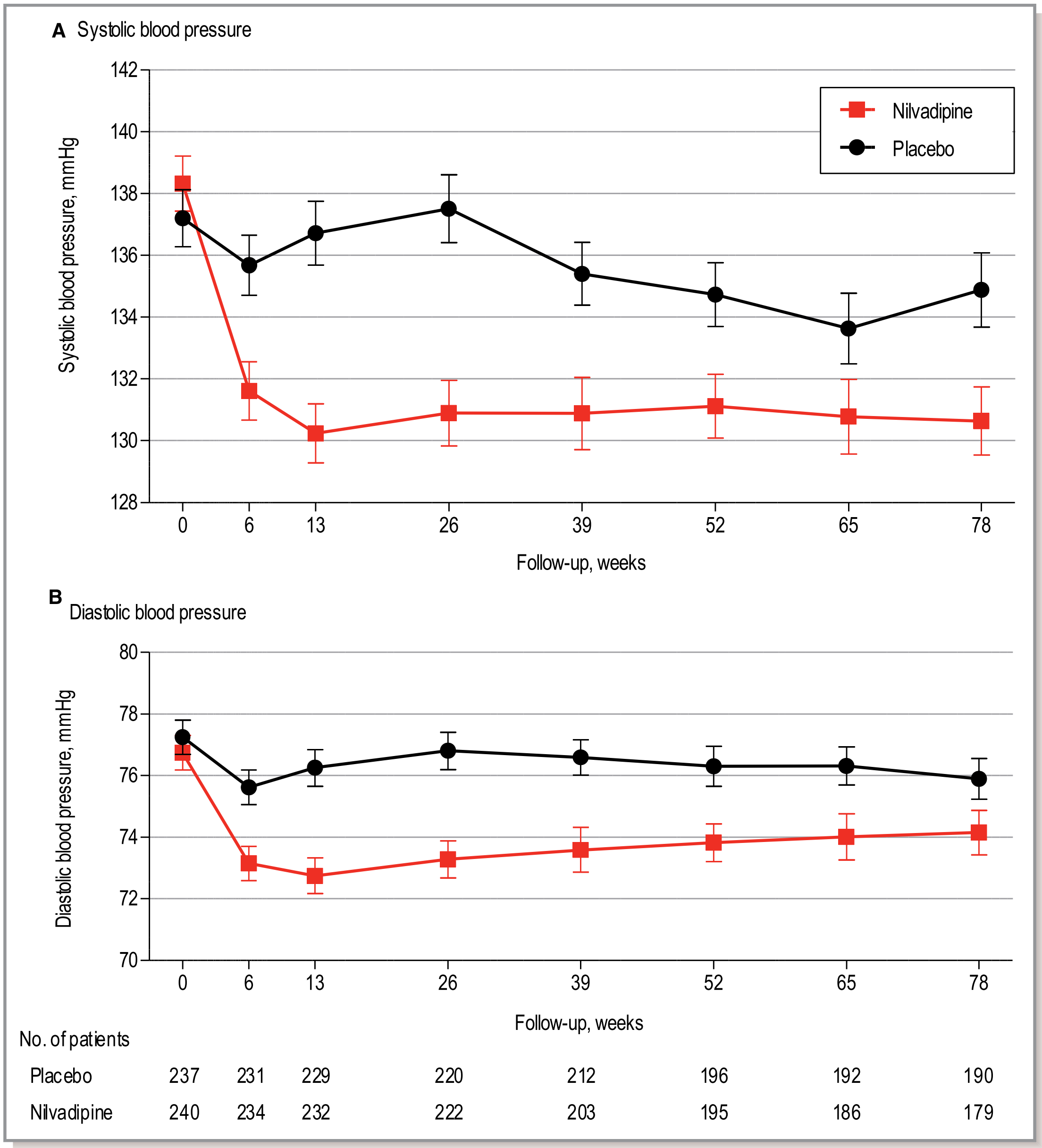


Figure 2. Effect of treatment on mean sitting SBP and DBP. Mean sitting SBP (**A**) and DBP (**B**) per visit and the number of patients included per visit. After 13 weeks of treatment, sitting SBP and DBP had fallen by -7.8 ± 14.0 and -3.9 ± 8.7 mm Hg for nilvadipine and by -0.4 ± 14.1 and -0.8 ± 9.1 mm Hg for placebo ($P<0.001$ for SBP and DBP). Error bars indicate SEM. DBP indicates diastolic blood pressure; No., number; SBP, systolic blood pressure.

Relationship Between Characteristics and OH

None of the investigated baseline patient characteristics were significant predictors of OH or moderated the effect of treatment on OH (Table S5). For example, there were no differences between patients with high, normal, or low BP at baseline, or between patients with higher or lower frailty index at baseline. Other baseline characteristics that were investigated included age, Mini-Mental State Examination score, diabetes mellitus, use of antihypertensives parallel to the intervention, use of antidepressants, and use of cholinesterase inhibitors.

Discussion

These secondary analyses of a randomized clinical trial investigated the effect of the antihypertensive agent nilvadipine on OH prevalence in patients with mild-to-moderate AD. In 477 patients, of whom 53% had grade I hypertension, a 78-week intervention with 8 mg of nilvadipine (± other antihypertensives) did not result in a significant increase of OH prevalence, determined with intermittent BP measurements while sitting and after 1 minute of standing. Moreover, the number of reported events of fractures, falls, syncope, and dizziness were similar between the groups. None of the

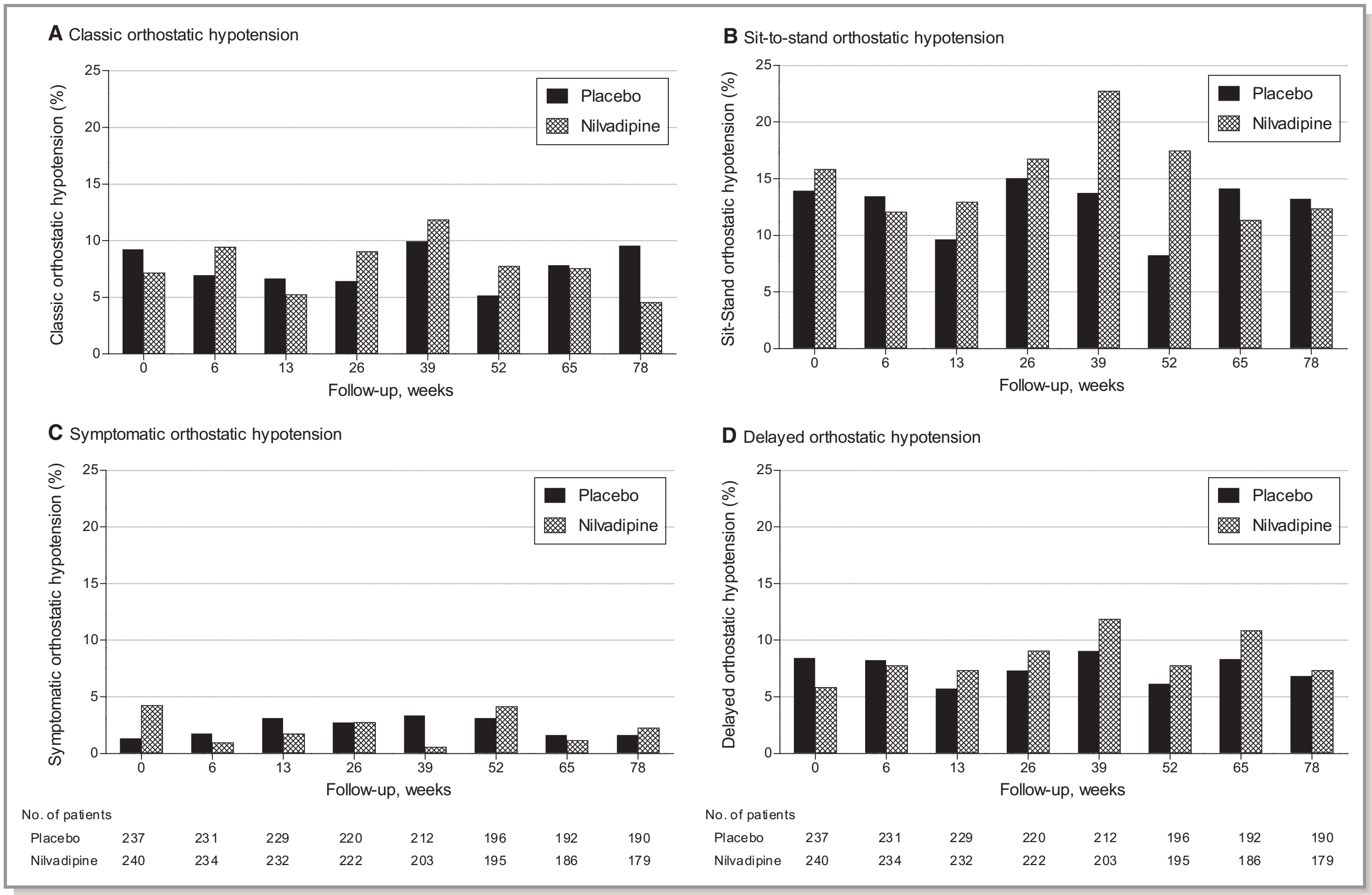


Figure 3. Effect of treatment on proportion of patients with orthostatic hypotension. Classic orthostatic hypotension (**A**): drop of ≥20 mm Hg in systolic BP or ≥10 mm Hg in diastolic BP after 1 minute (OR [95% CI] =1.1 [0.8–1.5], *P*=0.62). Sit-to-stand orthostatic hypotension (**B**): of ≥15 mm Hg in systolic BP or ≥7 mm Hg in diastolic BP after 1 minute (OR [95% CI] =1.2 [0.9–1.5], *P*=0.15). Symptomatic orthostatic hypotension (**C**): presence of symptoms upon standing, irrespective of drop in BP (OR [95% CI]=0.8 [0.3–2.3], *P*=0.67). Delayed orthostatic hypotension (**D**): presence of classic orthostatic hypotension after 5 minutes of standing (OR [95% CI]=1.2 [0.9–1.6], *P*=0.15). No. indicates number; OR, odds ratio.

predefined baseline characteristics moderated the relationship between nilvadipine and OH, indicating that there were no relevant subgroups for which the results might be different. These characteristics included age, frailty, or the use of other medications that could contribute to OH, such as antidepressants or cholinesterase inhibitors. Previous studies indicated an immediate effect of starting or intensifying antihypertensive treatment on falls and fractures in older people.[34,35] We did not see any short-term effects of our intervention after 6 weeks of treatment (Figure 3). Although not statistically significant, the upper limits of the CIs of our findings do not completely rule out a small effect of nilvadipine. However, as can be seen in Figures 3 and 4, the magnitude of such an effect would still not lie within clinically relevant margins.

The antihypertensive properties of nilvadipine are comparable to other, more common dihydropyridine calcium-channel blockers, such as nifedipine and amlopdipine.[21,22] Apart from that, it is known that the main determinant in reducing cardiovascular risk is the amount of BP reduction achieved and not the class of antihypertensive drug.[4,36,37] The BP reduction achieved in our study was moderate, but still falls within the range of BP reductions observed with other antihypertensives that successfully reduced cardiovascular events and mortality.[38]

It can be questioned whether the absence of a drug class effect in reducing cardiovascular risk is also applicable to the risk of OH. For β-blockers, treatment has been associated with an increased risk of OH,[39,40] which might be explained by their sympatholytic effects interfering with baroreflex-mediated BP recovery.[14,15,40] However, the efficacy and safety profile of β-blockers as first-line treatment of hypertension (in older patients) has already been questioned for other reasons.[4,41] For the remaining drug classes, a cross-sectional analysis from the TILDA (The Irish Longitudinal Study on Ageing) study found no differences in OH risk between single therapy with calcium-channel blockers, renin-angiotensin-aldosterone-system blockers, and diuretics, arguing against a drug class effect other than

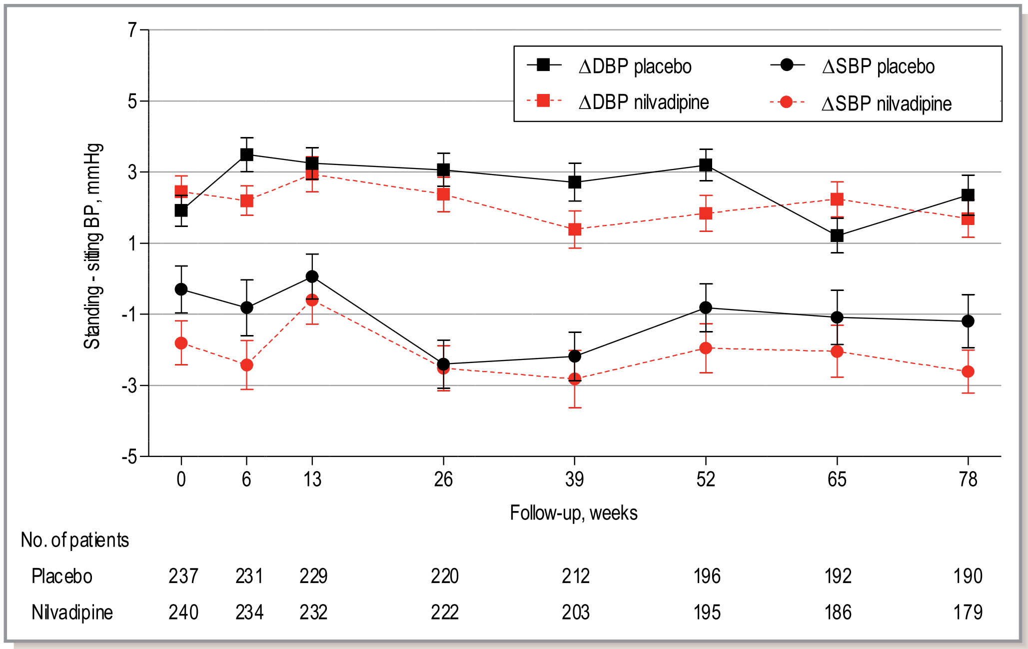


Figure 4. Effect of treatment on standing minus sitting BP. The figure displays ΔSBP (standing-sitting SBP) and ΔDBP (standing-sitting DBP) for nilvadipine and placebo at all visits. As can be seen in the figure, the mean ΔSBP is negative, indicating that standing SBP was lower than sitting SBP. The mean ΔDBP is positive, indicating that standing DBP was higher than sitting DBP. BP indicates blood pressure; DBP, diastolic blood pressure; No., number; SBP, systolic blood pressure.

β-blockers and thus favoring the extrapolation of nilvadipine to antihypertensive treatment in general.[40,42]

The hypothesis for a link between antihypertensive treatment and OH in older people has mainly emanated from findings of observational studies.[13] Evidence from randomized clinical trials is limited, especially in populations with cognitive impairment.[2] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (Type II diabetes mellitus, aged 62±7 years) and AASK (the African American Study of Kidney Disease and Hypertension) (black patients with kidney disease and hypertension, aged 54±10 years) trial found no effect of antihypertensive treatment on OH.[43,44] Subgroup analyses from SPRINT in people aged ≥75 years showed no difference in prevalence of OH, falls, or syncope between the intensive BP-lowering group and the standard treatment group.[17] Also HYVET (the Hypertension in the Very Elderly Trial) (aged ≥80 years) did not report a difference between the intervention (indapamide ± perindopril) and placebo group in sitting minus standing BP.[18] However, it has previously been recognized that participants of both SPRINT and HYVET were relatively fit and healthy and had no cognitive impairment or dementia,[3,45] hampering the extrapolation of their results to a more frail population. This is an important limitation, because frailty can decrease the ability to adequately respond to challenges (ie, antihypertensive treatment) and increase the risks of corresponding adverse outcomes (ie, OH).[28]

A slightly more vulnerable population was studied in the DANTE (Discontinuation of Antihypertensive Treatment in Elderly People) trial, which assessed the effect of deprescribing antihypertensive treatment in people aged ≥75 years with mild cognitive impairment.[46] Subgroup analyses found no convincing evidence that the prevalence of OH was reduced when antihypertensive medication was stopped and SBP increased by 4.3 mm Hg.[47] Our study results are in line with SPRINT, HYVET, and DANTE, but now in a population with mild-to-moderate AD, a group that has been excluded from previous trials. Although we recognize that cognitive impairment is just one, albeit a very dominant one, dimension of frailty,[28] this study contributes to understanding the effect of antihypertensive treatment on OH in a vulnerable population.

It has been suggested that OH in AD may be related to autonomic dysfunction instead of cardiovascular disease.[48] However, evidence for this is limited, and may have been biased by misclassification of Lewy body dementia as AD.[49] We recently demonstrated that baroreflex sensitivity was not impaired in mild-to-moderate AD, which would also argue against autonomic impairment in AD.[50]

Strengths and Limitations

Strengths of this study are the thorough design, standardized procedures, 100% monitoring, and low attrition rate, adding to

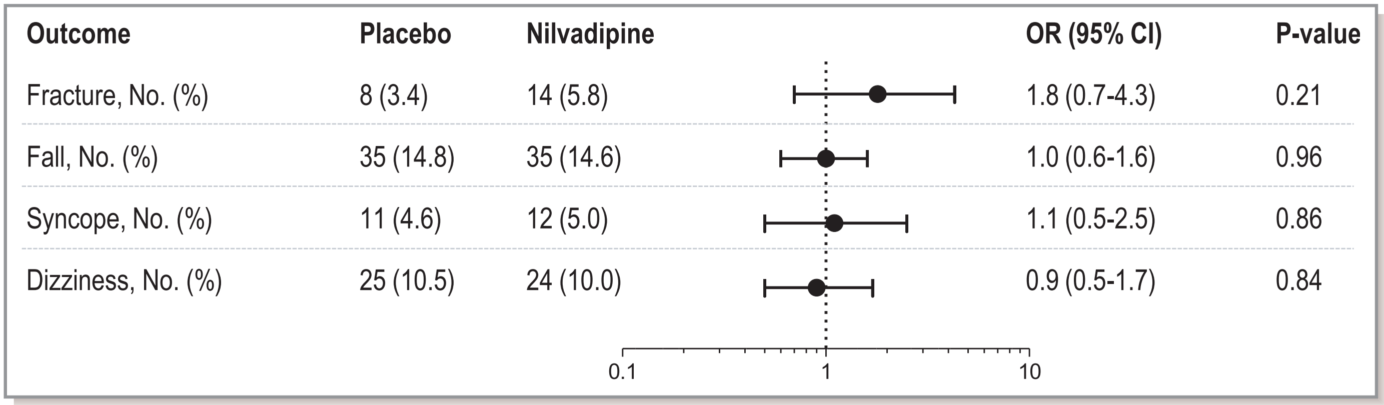


Figure 5. Effect of treatment on proportion of reported clinical outcomes related to orthostatic hypotension. Odds ratio results from logistics regression. No. indicates number; OR, odds ratio.

a high internal validity. Although these secondary analyses were not prespecified in the trial protocol, careful monitoring of BP, OH, and OH-related outcomes was a preplanned part of the study for safety reasons. Like any clinical trial, we are limited by the inclusion and exclusion criteria. This, for example, resulted in a relatively younger sample of AD patients compared with the general AD population, where >80% is older than 75 years. However, certain generalizability of our findings is still supported by the heterogeneity of baseline cognitive scores, frailty levels, age, and the fact that recruitment took place at both academic and general hospitals. Extrapolation to clinical AD populations is also aided by the fact that no biomarker evidence for AD (such as cerebrospinal fluid or positron emission tomography–amyloid imaging) was required, as such a requirement may lead to considerable selection bias (towards younger, less frail AD patients, and patients seen at tertiary centers). According to the recent Research Framework for AD of the National Institute on Aging and the Alzheimer's Association, our study population would be classified as "Alzheimer clinical syndrome."[51]

Patients were allowed to use concomitant medication (provided that it did not interfere with nilvadipine), including cholinesterase inhibitors and/or memantine and antidepressants. This enhances generalizability, because concomitant use of these drugs (for example, antidepressants) is not only common but also increases the risk of falls or OH.[52,53]

Baseline hypertension was not a requirement for inclusion, resulting in a study population that does not consist merely of patients who would normally qualify for antihypertensive treatment. However, sensitivity analyses showed the same result in those with baseline hypertension. Moreover, the absence of adverse effects at lower entry BP levels only strengthens our findings and attunes with the latest hypertension guidelines.[4]

External validity is limited by the exclusion of patients with severe hypertension (≥160/99 mm Hg). Also, baseline prevalence of OH was lower (8%) than previously reported in AD,[9] which might be an illustration of inclusion bias toward healthier patients. This is, however, not supported by the distribution of the cognitive scores and frailty.

We measured BP using intermittent BP measurements with patients sitting and 1 minute after they were standing. Although this deviates from the 3-minute guideline recommendation,[54] it was recently suggested that measuring after 1 minute correlates better with clinical outcomes.[55] Our choice to measure BP while patients were sitting rather than supine may have underestimated the prevalence of OH, because of reduced gravitational venous pooling. However, using the proposed diagnostic cut-off for sit-to-stand OH measurements resulted in similar findings.[32] Finally, the reliability of reporting adverse event and symptoms upon standing might be low in a population with cognitive impairment, possibly leading to underreporting. These concerns were in part mitigated, however, because we conducted regular semistructured interviews with the patient's caregiver.

Perspectives

The implications of our findings are 2-fold. First, our study adds to the discussion on the benefit-to-risk ratio of the use of antihypertensive medication in AD,[56] by providing hitherto missing evidence that OH risk is not exacerbated by treatment. Although more evidence is required, some patients with mild-to-moderate AD may still benefit from antihypertensive treatment. For instance, the average estimated survival after AD diagnosis is 3 to 9 years,[57] while positive effects of antihypertensive treatment in the elderly already become apparent after 1 year of treatment.[17,18] Furthermore, comorbidities, including cardiovascular and cerebrovascular events, can have detrimental effects on progression of AD, and are 1 of the major causes of death in AD.[58–60] Thus, withholding treatment in a patient with AD because of an overestimated fear of OH might negatively affect patient outcomes. Instead, we advocate that decisions regarding antihypertensive treatment should always be tailored to patient's preferences and physical and mental status.[56]

Another implication of our findings is that they add to the complex debate on the use of antihypertensive medication in vulnerable older people,[6] of which this AD population is an important example. It is a persistent belief among many physicians that treating older people with antihypertensive medication would do more harm than good.[7] The current study has recruited, to date, the most vulnerable population and found that treatment with a low-dose calcium-channel blocker led to an effective, moderate BP reduction without causing harm in the sense of OH, or OH-related adverse outcomes such as falls or fractures.

Conclusions

In patients with mild-to-moderate AD, with or without hypertension, 78-week treatment with 8 mg of the calcium-channel blocker nilvadipine did not significantly increase the risk of OH, fractures, falls, syncope, and dizziness. We provide evidence that starting or adding a low dose of antihypertensive treatment is safe with respect to OH and clinical outcomes. Trials that are primarily designed to investigate patient-relevant beneficial as well as adverse outcomes of antihypertensive treatment are required to elicit the full benefit-to-risk balance in this quickly growing patient group.

Appendix

The Nilvad Study Group includes, in addition to the authors in the by-line: Ricardo Segurado, CSTAR and School of Public Health, Physiotherapy and Sport Science, University College Dublin (UCD), Dublin, Ireland; Sean Kennelly, Department of Age Related Healthcare, Tallaght Hospital, Dublin 24 and Department of Medical Gerontology, Trinity College Dublin; Robert Howard, Division of Psychiatry, University College London and King's College London; Florence Pasquier, CHU Lille, Univ. Lille, DISTALZ Laboratory of Excellence, F-59000 Lille, France; Anne Börjesson-Hanson, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg; Magda Tsolaki, Papanikolaou General Hospital of Thessaloniki, Greece; Ugo Lucca, Laboratory of Geriatric Neuropsychiatry, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; D. William Molloy, University College Cork Centre for Gerontology and Rehabilitation, Cork, Ireland; Robert Coen, Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland; Matthias W. Riepe, Department of Geriatrics and Old Age Psychiatry, Psychiatry II, Ulm University at BKH Günzburg, Germany; János Kálmán, Department of Psychiatry, University of Szeged, Hungary; Rose Anne Kenny, Department of Medical Gerontology, Trinity College Dublin (TCD), Dublin, Ireland; Fiona Cregg, Department of Medical Gerontology, Trinity College Dublin (TCD), Dublin, Ireland; Sarah O'Dwyer, Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland; Cathal Walsh, Health Research Institute and MACSI, Department of Mathematics and Statistics, University of Limerick, Ireland; Jessica Adams, Department of Old Age Psychiatry, King's College London; Rita Banzi, Laboratory of Geriatric Neuropsychiatry, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; Laetitia Breuilh, CHU Lille, Univ. Lille, DISTALZ Laboratory of Excellence, F-59000 Lille, France; Leslie Daly, CSTAR and School of Public Health, Physiotherapy and Sport Science, University College Dublin (UCD), Dublin, Ireland; Suzanne Hendrix, Pentara Corporation, 2180 Claybourne Avenue, Salt Lake City, UT 84109, USA; Paul Aisen, Department of Neurology, University of Southern California; Siobhan Gaynor, Molecular Medicine Ireland (MMI), Dublin, Ireland; Ali Sheikhi, Health Research Institute and MACSI, Department of Mathematics and Statistics, University of Limerick, Ireland; Diana G. Taekema, Department of Geriatric Medicine, Rijnstate Hospital, Arnhem, The Netherlands; Frans R. Verhey, Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, The Netherlands; Raffaello Nemni, IRCCS Don Gnocchi Foundation-University of Milan, Italy; Flavio Nobili, Dept. of Neuroscience (DINOGMI), University of Genoa, and IRCCS AOU Polyclinic, Hospital San Martino, Genoa, Italy; Massimo Franceschi, Neurology Department, Multimedica, Castellanza, Italy; Giovanni Frisoni, Centro San Giovanni di Dio—IRCCS Fatebenefratelli, Brescia, Italy; Orazio Zanetti, Centro San Giovanni di Dio—IRCCS Fatebenefratelli, Brescia, Italy; Anastasia Konsta, Aristotle University of Thessaloniki (AUTH), First Psychiatric Department, Papageorgiou General Hospital, Greece; Orologas Anastasios, Ahepa University General Hospital of Thessaloniki, Greece; Styliani Nenopoulou, Papanikolaou General Hospital of Thessaloniki, Greece; Fani Tsolaki-Tagaraki, Papanikolaou General Hospital of Thessaloniki, Greece; Magdolna Pakaski, Department of Psychiatry, University of Szeged, Hungary; Olivier Dereeper, Centre Hospitalier de Calais, France; Vincent de la Sayette, Centre Hospitalier Universitaire de Caen, France; Olivier Sénéchal, Centre Hospitalier de Lens, France; Isabelle Lavenu, Centre Hospitalier de Béthune, France; Agnès Devendeville, Centre Hospitalier Universitaire d'Amiens, France; Gauthier Calais, Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), France; Fiona Crawford, Archer Pharmaceuticals Inc., 2040 Whitfield Avenue, Sarasota, Florida, USA and Roskamp Institute, Sarasota, Florida, USA; Michael Mullan, Archer Pharmaceuticals Inc., 2040 Whitfield Avenue,

Sarasota, Florida, USA and Roskamp Institute, Sarasota, Florida, USA; Pauline Aalten, Ph.D., Department of Psychiatry and Neuropsychology, School of Mental Health and Neurosciences, Alzheimer Center Limburg, Maastricht University, Maastricht, The Netherlands; Maria A. Berglund, R.N., Sahlgrenska University Hospital, Gotheburg, Sweden; Daan L. K. de Jong, M.Sc., Radboud university medical center, Donders Institute for Brain Cognition and Behaviour, Department of Geriatric Medicine, Radboud Alzheimer Center, Nijmegen, The Netherlands; Olivier Godefroy, M.D., Ph.D., Centre Hospitalier Universitaire d'Amiens, France; Siobhan Hutchinson, M.D., St. James's Hospital, Dublin, Ireland; Aikaterini Ioannou, M.D. 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Michael Jonsson, M.D., Ph.D., Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; Annette Kent, Ph.D., Trinity College Dublin (TCD), Dublin, Ireland; Jürgen Kern, M.D., Ph.D., Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; Petros Nemtsas, M.D., Ph.D., 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Minoa-Kalliopi Panidou, B.Sc., M.A., 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Laila Abdullah, Ph.D., Archer Pharmaceuticals Inc, 2040 Whitfield Avenue, Sarasota, Florida, USA; Daniel Paris, Ph.D., Archer Pharmaceuticals Inc, 2040 Whitfield Avenue, Sarasota, Florida, USA; Gerrita J. van Spijker, M.Sc., Radboud university medical center, Donders Institute for Brain Cognition and Behaviour, Department of Geriatric Medicine, Radboud Alzheimer Center, Nijmegen, The Netherlands; Martha Spiliotou, M.D., Ph.D., 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Georgia Thomoglou, B.Sc., 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Anders Wallin, M.D., Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden.

Acknowledgments

We are grateful to all study participants and their caregivers for their time and effort. We thankfully acknowledge the support of all individuals who conducted the Nilvad trial at the study sites. We thank Alzheimer Europe and Newsweaver who helped with dissemination and promotion of the trial and GABO:mi Gesellschaft für Ablauforganisation :milliarium mbH & Co. KG who were the project management company for the majority of the trial. We acknowledge the time and effort contributed by Muireann O'Briain; Oliver Gupta; the members of the Ethics Advisory Board (Ursula Collins, Mary Donnelly, Tony O'Brien, and Shaun O'Keefe); the members of Scientific Advisory Board (Paul Aisen, Suzanne Hendrix, Robin Jacoby, and Maurice O'Connell); and the members of the Data Safety Monitoring Board (Bernadette McGuinness, John Newell, Martin O'Donnell, and Peter Passmore).

Sources of Funding

The Nilvad study was funded by the European Commission Framework 7 Programme Health Theme Collaborative Project (grant 279093, awarded to Lawlor, Principal Investigator). In addition, Heus and Claassen received support from the Alzheimer's Drug Discovery Foundation (grant 20121210) and from the Dutch Alzheimer Society (grant WE.09-2015-03) to conduct the work reported in this publication. The European Commission Framework 7 Programme, the Alzheimer's Drug Discovery Foundation, and the Dutch Alzheimer Society had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

Lawlor is named as inventor in a pending patent for the use of nilvadipine based on the results of the main Nilvad clinical trial. The remaining authors have no disclosures to report.

References

1. Welsh TJ, Gladman JR, Gordon AL. The treatment of hypertension in people with dementia: a systematic review of observational studies. *BMC Geriatr*. 2014;14:19.
2. van der Wardt V, Logan P, Conroy S, Harwood R, Gladman J. Antihypertensive treatment in people with dementia. *J Am Med Dir Assoc*. 2014;15:620–629.
3. Benetos A. How to obtain more evidence for the management of hypertension in frail patients over 80 years old? *Eur Geriatr Med*. 2018;9:137– 140.
4. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 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. *Hypertension*. 2017;72:e33.
5. Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med*. 2017;166:430–437.
6. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A, Redon J, Grodzicki T, Dominiczak A, Strandberg T, Mancia G. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the management of hypertension in very old, frail subjects. *Hypertension*. 2016;67:820–825.
7. Hajjar I, Miller K, Hirth V. Age-related bias in the management of hypertension: a national survey of physicians' opinions on hypertension in elderly adults. *J Gerontol A Biol Sci Med Sci*. 2002;57:M487–M491.
8. Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, Cronin H, Kenny RA. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). *Circulation*. 2014;130:1780–1789.

9. Mehrabian S, Duron E, Labouree F, Rollot F, Bune A, Traykov L, Hanon O. Relationship between orthostatic hypotension and cognitive impairment in the elderly. *J Neurol Sci*. 2010;299:45–48.
10. Finucane C, O'Connell MD, Donoghue O, Richardson K, Savva GM, Kenny RA. Impaired orthostatic blood pressure recovery is associated with unexplained and injurious falls. *J Am Geriatr Soc*. 2017;65:474–482.
11. Angelousi A, Girerd N, Benetos A, Frimat L, Gautier S, Weryha G, Boivin JM. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. *J Hypertens*. 2014;32:1562–1571; discussion 1571.
12. McNicholas T, Tobin K, Carey D, O'Callaghan S, Kenny RA. Is baseline orthostatic hypotension associated with a decline in global cognitive performance at 4-year follow-up? data from TILDA (The Irish Longitudinal Study on Ageing). *J Am Heart Assoc*. 2018;7:e008976. DOI: 10.1161/JAHA.118.008976.
13. Frith J, Parry SW. New horizons in orthostatic hypotension. *Age Ageing*. 2017;46:168–174.
14. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic hypotension and medication use in the British women's heart and health study. *Age Ageing*. 2010;39:51–56.
15. Valbusa F, Labat C, Salvi P, Vivian ME, Hanon O, Benetos A. Orthostatic hypotension in very old individuals living in nursing homes: the PARTAGE study. *J Hypertens*. 2012;30:53–60.
16. Zia A, Kamaruzzaman SB, Myint PK, Tan MP. The association of antihypertensives with postural blood pressure and falls among seniors residing in the community: a case-control study. *Eur J Clin Invest*. 2015;45:1069–1076.
17. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged >/=75 years: a randomized clinical trial. *JAMA*. 2016;315:2673–2682.
18. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898.
19. Lawlor B, Kennelly S, O'Dwyer S, Cregg F, Walsh C, Coen R, Kenny RA, Howard R, Murphy C, Adams J, Daly L, Segurado R, Gaynor S, Crawford F, Mullan M, Lucca U, Banzi R, Pasquier F, Breuilh L, Riepe M, Kalman J, Wallin A, Borjesson A, Molloy W, Tsolaki M, Olde Rikkert M. NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease. *BMJ Open*. 2014;4:e006364.
20. Lawlor B, Segurado R, Kennelly S, Olde Rikkert MGM, Howard R, Pasquier F, Borjesson-Hanson A, Tsolaki M, Lucca U, Molloy DW, Coen R, Riepe MW, Kalman J, Kenny RA, Cregg F, O'Dwyer S, Walsh C, Adams J, Banzi R, Breuilh L, Daly L, Hendrix S, Aisen P, Gaynor S, Sheikhi A, Taekema DG, Verhey FR, Nemni R, Nobili F, Franceschi M, Frisoni G, Zanetti O, Konsta A, Anastasios O, Nenopoulou S, Tsolaki-Tagaraki F, Pakaski M, Dereeper O, de la Sayette V, Senechal O, Lavenu I, Devendeville A, Calais G, Crawford F, Mullan M. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. *PLoS Med*. 2018;15:e1002660.
21. Rosenthal J. Nilvadipine: profile of a new calcium antagonist. An overview. *J Cardiovasc Pharmacol*. 1994;24(suppl 2):S92–S107.
22. Leonetti G. Effects of nilvadipine and amlodipine in patients with mild to moderate essential hypertension: a double blind, prospective, randomised clinical trial. *Curr Med Res Opin*. 2005;21:951–958.
23. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7:263–269.
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
25. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356–1364.
26. Gauthier S, Gelinas I, Gauthier L. Functional disability in alzheimer's disease. *Int Psychogeriatr*. 1997;9(suppl 1):163–165.
27. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412–2414.
28. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24.
29. Meulenbroek O, O'Dwyer S, de Jong D, van Spijker G, Kennelly S, Cregg F, Olde Rikkert M, Abdullah L, Wallin A, Walsh C, Coen R, Kenny RA, Daly L, Segurado R, Borjesson-Hanson A, Crawford F, Mullan M, Lucca U, Banzi R, Pasquier F, Breuilh L, Riepe M, Kalman J, Molloy W, Tsolaki M, Howard R, Adams J, Gaynor S, Lawlor B. European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease-the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD cerebrospinal fluid biomarkers; NILVAD cerebral blood flow. *BMJ Open*. 2016;6:e011584.
30. Pajewski NM, Williamson JD, Applegate WB, Berlowitz DR, Bolin LP, Chertow GM, Krousel-Wood MA, Lopez-Barrera N, Powell JR, Roumie CL, Still C, Sink KM, Tang R, Wright CB, Supiano MA; for the SSRG. Characterizing frailty status in the systolic blood pressure intervention trial. *J Gerontol A Biol Sci Med Sci*. 2016;71:649–655.
31. Schatz IJ, Bannister R, Goetz CG. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46:1470.
32. Shaw BH, Garland EM, Black BK, Paranjape SY, Shibao CA, Okamoto LE, Gamboa A, Diedrich A, Plummer WD, Dupont WD, Biaggioni I, Robertson D, Raj SR. Optimal diagnostic thresholds for diagnosis of orthostatic hypotension with a 'sit-to-stand test'. *J Hypertens*. 2017;35:1019–1025.
33. R Core Team. *R: a language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. Available at: http://www.R-project.org/. Accessed May 11, 2019.
34. Shimbo D, Barrett Bowling C, Levitan EB, Deng L, Sim JJ, Huang L, Reynolds K, Muntner P. Short-term risk of serious fall injuries in older adults initiating and intensifying treatment with antihypertensive medication. *Circ Cardiovasc Qual Outcomes*. 2016;9:222–229.
35. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med*. 2012;172:1739–1744.
36. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.
37. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A, Heritier S, Li N, Perkovic V, Woodward M, MacMahon S. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008;336:1121–1123.
38. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: a critical reappraisal. *Circ Res*. 2015;116:1058–1073.
39. Juraschek SP, Appel LJ, Miller ER III, Mukamal KJ, Lipsitz LA. Hypertension treatment effects on orthostatic hypotension and its relationship with cardiovascular disease. *Hypertension*. 2018;72:986–993.
40. Canney M, O'Connell MDL, Murphy CM, O'Leary N, Little MA, O'Seaghdha CM, Kenny RA. Single agent antihypertensive therapy and orthostatic blood pressure behaviour in older adults using beat-to-beat measurements: the Irish longitudinal study on ageing. *PLoS One*. 2016;11:e0146156.
41. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2012;11:CD002003.
42. Romero-Ortuno R, O'Connell MD, Finucane C, Soraghan C, Fan CW, Kenny RA. Insights into the clinical management of the syndrome of supine hypertension–orthostatic hypotension (SH-OH): The Irish Longitudinal Study on Ageing (TILDA). *BMC Geriatr*. 2013;13:73.
43. Juraschek SP, Miller ER III, Appel LJ. Orthostatic hypotension and symptoms in the AASK trial. *Am J Hypertens*. 2018;31:665–671.
44. Fleg JL, Evans GW, Margolis KL, Barzilay J, Basile JN, Bigger JT, Cutler JA, Grimm R, Pedley C, Peterson K, Pop-Busui R, Sperl-Hillen J, Cushman WC. Orthostatic hypotension in the accord (action to control cardiovascular risk in diabetes) blood pressure trial: prevalence, incidence, and prognostic significance. *Hypertension*. 2016;68:888–895.
45. Sexton DJ, Canney M, O'Connell ML, Moore P, Little MA, O'Seaghdha CM, Kenny RA. Injurious falls and syncope in older community-dwelling adults meeting inclusion criteria for sprint. *JAMA Intern Med*. 2017;177:1385–1387.
46. Moonen JE, Foster-Dingley JC, de Ruijter W, van der Grond J, Bertens AS, van Buchem MA, Gussekloo J, Middelkoop HA, Wermer MJ, Westendorp RG, de Craen AJ, van der Mast RC. Effect of discontinuation of

antihypertensive treatment in elderly people on cognitive functioning—the DANTE Study Leiden: a randomized clinical trial. *JAMA Intern Med*. 2015;175:1622–1630.

47. Moonen JE, Foster-Dingley JC, de Ruijter W, van der Grond J, de Craen AJ, van der Mast RC. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE study Leiden. *Age Ageing*. 2016;45:249–255.
48. Femminella GD, Rengo G, Komici K, Iacotucci P, Petraglia L, Pagano G, de Lucia C, Canonico V, Bonaduce D, Leosco D, Ferrara N. Autonomic dysfunction in Alzheimer's disease: tools for assessment and review of the literature. *J Alzheimer's Dis*. 2014;42:369–377.
49. McKeith IG, Ballard CG, Perry RH, Ince PG, O'Brien JT, Neill D, Lowery K, Jaros E, Barber R, Thompson P, Swann A, Fairbairn AF, Perry EK. Prospective validation of consensus criteria for the diagnosis of dementia with lewy bodies. *Neurology*. 2000;54:1050–1058.
50. de Heus RAA, de Jong DLK, Sanders ML, van Spijker GJ, Oudegeest-Sander MH, Hopman MT, Lawlor BA, Olde Rikkert MGM, Claassen J. Dynamic regulation of cerebral blood flow in patients with Alzheimer disease. *Hypertension*. 2018;72:139–150.
51. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimer's Dement*. 2018;14:535–562.
52. Darowski A, Chambers SA, Chambers DJ. Antidepressants and falls in the elderly. *Drugs Aging*. 2009;26:381–394.
53. Briggs R, Carey D, McNicholas T, Claffey P, Nolan H, Kennelly SP, Kenny RA. The association between antidepressant use and orthostatic hypotension in older people: a matched cohort study. *J Am Soc Hypertens*. 2018;12:597–604.
54. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz IJ, Schondorf R, Stewart JM, van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Auton Neurosci*. 2011;161:46–48.
55. Juraschek SP, Daya N, Rawlings AM, Appel LJ, Miller ER III, Windham BG, Griswold ME, Heiss G, Selvin E. Association of history of dizziness and long-term adverse outcomes with early vs later orthostatic hypotension assessment times in middle-aged adults. *JAMA Intern Med*. 2017;177:1316–1323.
56. Harrison JK, Van Der Wardt V, Conroy SP, Stott DJ, Dening T, Gordon AL, Logan P, Welsh TJ, Taggar J, Harwood R, Gladman JRF. New horizons: the management of hypertension in people with dementia. *Age Ageing*. 2016;45:740–746.
57. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jönsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H. Defeating Alzheimer's disease and other dementias: a priority for European Science and Society. *Lancet Neurol*. 2016;15:455–532.
58. Coutu JP, Lindemer ER, Konukoglu E, Salat DH. Two distinct classes of degenerative change are independently linked to clinical progression in mild cognitive impairment. *Neurobiol Aging*. 2017;54:1–9.
59. Haaksma ML, Vilela LR, Marengoni A, Calderon-Larranaga A, Leoutsakos JS, Olde Rikkert MGM, Melis RJF. Comorbidity and progression of late onset Alzheimer's disease: a systematic review. *PLoS One*. 2017;12:e0177044.
60. Villarejo A, Benito-Leon J, Trincado R, Posada IJ, Puertas-Martin V, Boix R, Medrano MR, Bermejo-Pareja F. Dementia-associated mortality at thirteen years in the NEDICES Cohort Study. *J Alzheimer's Dis*. 2011;26:543–551.

SUPPLEMENTAL MATERIAL

Table S1. Composition of the Frailty Index.

#	Item	Response	Score	Notes
1	Gait speed	≥ 0.67 m/s	0	
		< 0.67 m/s	1	
2	Use of a walking aid when performing gait speed test	No	0	
		Yes	1	
3	Polypharmacy, based on trial record of concomitant medication	≤5	0	
		6	0.2	
		7	0.4	
		8	0.6	
		9	0.8	
		≥10	1	
4	Body Mass Index	18.5 – 29.9	0	
		<18.5	1	
		≥ 30	1	
5	3 items from ADAS-cog combined: - Spoken language ability - Comprehension - Word finding in spontaneous speech	No difficulty	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Very mild difficulty	0.2	
		Mild difficulty	0.4	
		Moderate difficulty	0.6	
		Moderate-severe difficulty	0.8	
		Severe difficulty	1.0	
6	2 items from CDR combined: - Memory - Orientation	No problem	0	Take the sum of the original items, categorize to: ≤1.0= 0; 1.5= 0.17; 2.0= 0.33; 2.5= 0.50; 3.0= 0.67; 3.5= 0.83; ≥4.0= 1
		Probably a problem	0.5	
		Mild problem	1	
		Moderate problem	2	
		Severe problem	3	
7	3 items about contact with family from the LSNS combined: - Number of relatives seen or called once a month - Number of relatives to call for help - Number of relatives to talk about private things	None	1	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		1 person	0.8	
		2 persons	0.6	
		3-4 persons	0.4	
		5-9 persons	0.2	
		>9 persons	0	
8	3 items about contact with friends from the LSNS combined: - Number of friends seen or called once a month - Number of friends to call for help - Number of friends to talk about private things	None	1	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		1 person	0.8	
		2 persons	0.6	
		3-4 persons	0.4	
		5-9 persons	0.2	
		>9 persons	0	
9	3 items about taking a bath or shower combined: - Undertake a bath or a shower	Able without help	0	Take the sum of the original items / number of filled
		Not able without help	1	

	- Prepare utilities needed to take a bath or shower - Wash and dry body parts completely and safely			items (0 = no deficit, 1=full deficit)
10	2 items about taking care of hair: - Decide to care hair - Caring hair	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
11	5 items about getting dressed completely and appropriately: - Undertake to dress - Choose appropriate clothing - Dress in appropriate order - Dress completely - Undress completely	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
12	2 items about eating: - Choose appropriate seasoning and utensils - Eat appropriately	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
13	3 items about preparing a light meal: - Undertake to prepare a light meal - Plan a light meal - Cook a light meal safely	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
14	3 items about using the telephone: - Attempt to telephone at a suitable time - Dial a telephone correctly - Conduct telephone conversation appropriately	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
15	4 items about travelling or doing an outing: - Undertake to go out at appropriate time - Adequaltely organize an outgoing - Go out and reach destination without getting lost - Safely take adequate mode of transportation	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
16	3 items about managing finances: - Show interest in personal finance - Organise peronsal finance - Handle money correctly	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
17	2 items about taking medication: - Decide to take medication at correct time - Take medication as prescribed	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit,
		Not able without help	1	

				1=full deficit)
18	3 items about performing household tasks: - Show interest in performing household - Plan to perform household - Perform household correctly	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
19	2 items for urinary incontinence: - Decide to use the toilet appropriately - Use toilet without accidents	Able without help	0	Take the sum of the original items / number of filled items (0 = no deficit, 1=full deficit)
		Not able without help	1	
20	History of cerebrovascular disease	None	0	
		Present	1	
21	History of chronice pulmonary disease	None	0	
		Present	1	
22	History of congestive heart failure	None	0	
		Present	1	
23	History of cancer	None	0	
		Present	1	
24	History of cardiovascular disease	None	0	
		Present	1	
25	History of renal disease	None	0	
		Present	1	
26	History of diabetes	None	0	
		Without end organ damage	0.5	
		With end organ damage	1	

Measurement instrument for items 9 t/m 19 was DAD questionnaire. Measurement instrument for items 20 t/m 26 was Charlson's Comorbidity Index. ADAS-cog= Alzheimer's disease Assessment Scale - cognitive subscale; CDR= Clinical Dementia Rating; LSNS= Lubben Social Network Scale; DAD= Disability Assessment for Dementia questionnaire.

Table S2. Patient demographics and characteristics for complete cases.

Characteristic	Placebo	Nilvadipine
n	167	164
Women, No. (%)	91 (54.5)	114 (69.5)
Age, mean (SD), y	71.0 (7.5)	71.0 (8.5)
Time since diagnosis of AD, median (IQR), y	0.8 (0.3-2.1)	1.2 (0.5-2.1)
Mini-Mental State Examination score, mean (SD)	20.7 (3.8)	20.3 (3.6)
AD Assessment Scale-cognitive subscale, mean (SD)	34.7 (10.7)	33.9 (10.0)
Clinical Dementia Rating-sum of boxes, mean (SD)	5.1 (2.7)	5.1 (2.7)
Frailty index* median (IQR)	0.16 (0.1-0.3)	0.17 (0.1-0.2)
Sitting systolic blood pressure, mean (SD), mmHg	137.0 (14.3)	138.0 (13.0)
Sitting diastolic blood pressure, mean (SD), mmHg	77.4 (8.5)	76.9 (8.4)
Resting hear rate, mean (SD), beats per min	69.2 (9.6)	70.1 (10.5)
Classic orthostatic hypotension, No. (%)	16 (9.6)	9 (5.5)
Sit-to-stand orthostatic hypotension, No. (%)	24 (14.4)	25 (15.2)
Symptomatic orthostatic hypotension, No. (%)	3 (1.8)	7 (4.3)
Delayed orthostatic hypotension, No. (%)	15 (9.0)	9 (5.5)
Δ systolic blood pressure, mean (SD), mmHg	-1.02 (9.46)	-1.70 (10.39)
Δ systolic blood pressure, mean (SD), %	-0.58 (6.86)	-1.07 (7.58)
Use of medication at study enrollment, No. (%)		
At least 1 antihypertensiv medication, No. (%)	62 (37.1)	52 (31.7)
Cholinesterase inhibitors, No. (%)	149 (89.2)	145 (88.4)
Memantine, No. (%)	47 (28.1)	40 (24.4)
Antidepressants, No. (%)	65 (38.9)	58 (35.4)
Statins, No. (%)	58 (34.7)	50 (30.5)
Antithrombotics, No (%)	48 (28.7)	36 (22.0)
History of CVD, No. (%)	12 (7.2)	9 (5.5)
Diabetes, No. (%)	4 (2.4)	16 (9.6)

* n=154 placebo, n=150 nilvadipine (consented to Nilvad frailty-substudy). AD=Alzheimer's disease; CVD=cardiovascular disease.

Table S3. In- and exclusions from the per protocol analysis per follow-up visit.

Placebo (n=237)					
Week No.	**Included, No. (%)**	**Excluded, No. (%)**			
		Off IMP	*Not compliant*	*Missing BP*	*Deceased*
6	231 (97.5)	0 (0.0)	5 (2.1)	1 (0.4)	0 (0.0)
13	229 (96.6)	2 (0.8)	5 (2.1)	1 (0.4)	0 (0.0)
26	220 (92.8)	7 (3.0)	8 (3.4)	1 (0.4)	1 (0.4)
39	212 (89.5)	12 (5.1)	10 (4.2)	1 (0.4)	2 (0.8)
52	196 (82.7)	25 (10.5)	14 (5.9)	0 (0.0)	2 (0.8)
65	192 (81.0)	30 (12.7)	12 (5.1)	0 (0.0)	3 (1.3)
78	190 (80.2)	34 (14.3)	9 (3.8)	1 (0.4)	3 (1.3)
Nilvadipine (n=240)					
Week No.	**Included, No. (%)**	**Excluded, No. (%)**			
		Off IMP	*Not compliant*	*Missing BP*	*Deceased*
6	234 (97.5)	0 (0.0)	5 (2.1)	1 (0.4)	0 (0.0)
13	232 (96.7)	2 (0.8)	5 (2.1)	1 (0.4)	0 (0.0)
26	222 (92.5)	12 (5.0)	5 (2.1)	0 (0.0)	1 (0.4)
39	203 (84.6)	25 (10.4)	9 (3.8)	2 (0.8)	1 (0.4)
52	195 (81.3)	37 (15.4)	5 (2.1)	1 (0.4)	2 (0.8)
65	186 (77.5)	43 (17.9)	7 (2.9)	2 (0.8)	2 (0.8)
78	179 (74.6)	47 (19.6)	8 (3.3)	4 (1.7)	2 (0.8)

Not compliant indicates a compliance <80% in the 3-month window preceding the visit (6-week window for the week 6 visit). IMP= investigational medicinal product; BP=blood pressure.

.

Table S4. Effect of treatment on orthostatic hypotension.

	Per protocol	Complete cases
Logistic regression models	**OR [95% CI], *P***	**OR [95% CI], *P***
Classic OH	1.1 [0.8 - 1.5], 0.62	1.1 [0.8 - 1.6], 0.55
Sit-to-stand OH	1.2 [0.9 - 1.5], 0.15	1.2 [0.9 - 1.7], 0.13
Symptomatic OH	0.8 [0.3 - 2.3], 0.67	0.9 [0.2 - 3.4], 0.84
Delayed OH	1.2 [0.9 - 1.6], 0.15	1.3 [0.9 - 1.8], 0.19
Independent samples t-test	**mean diff. [95% CI], *P***	**mean diff. [95% CI], *P***
Classic OH	-0.4 [-2.7 - 1.9], 0.72	-0.8 [-3.3 - 1.7], 0.52
Sit-to-stand OH	-2.7 [-5.8 - 0.4], 0.09	-2.6 [-5.8 - 0.7], 0.12
Symptomatic OH	0.7 [-0.6 - 2.0], 0.31	0.1 [-1.3 - 1.4], 0.94
Delayed OH	-1.1 [-3.5 - 1.3], 0.36	-1.7 [-4.3 - 0.9], 0.20
Linear regression models	**β [95% CI], *P***	**β [95% CI], *P***
ΔSBP, mmHg	-0.8 [-1.7 - 0.2], 0.13	-1.1[-2.2 - 0.0], 0.04
ΔSBP, %	-0.6 [-1.3 - 0.2], 0.12	-0.9 [-1.7- -0.1], 0.04

Logistic regression models report the odds ratio of treatment after correction for baseline ΔSBP and with random intercepts for patient and study centre. Independent samples t-test report the mean difference between groups for the proportion of visits during which a patient met criteria for OH. Classic OH: drop of ≥20 mmHg in systolic BP or ≥10 mmHg in diastolic BP after 1 minute. Sit-to-stand OH: drop of ≥15 mmHg in systolic BP or ≥7 mmHg in diastolic BP after 1 minute. Symptomatic OH: presence of symptoms upon standing, irrespective of the drop in BP. Delayed OH: presence of classic OH after 5 minutes of standing. Linear regression models report bèta of treatment after correction for baseline ΔSBP with random intercept for patient and study centre. ΔSBP: change in systolic blood pressure from sitting to standing expressed in mmHg and in % from sitting systolic blood pressure.

OR, oddds ratio; CI, confidence interval; OH, orthostatic hypotension; SBP, systolic blood pressure.

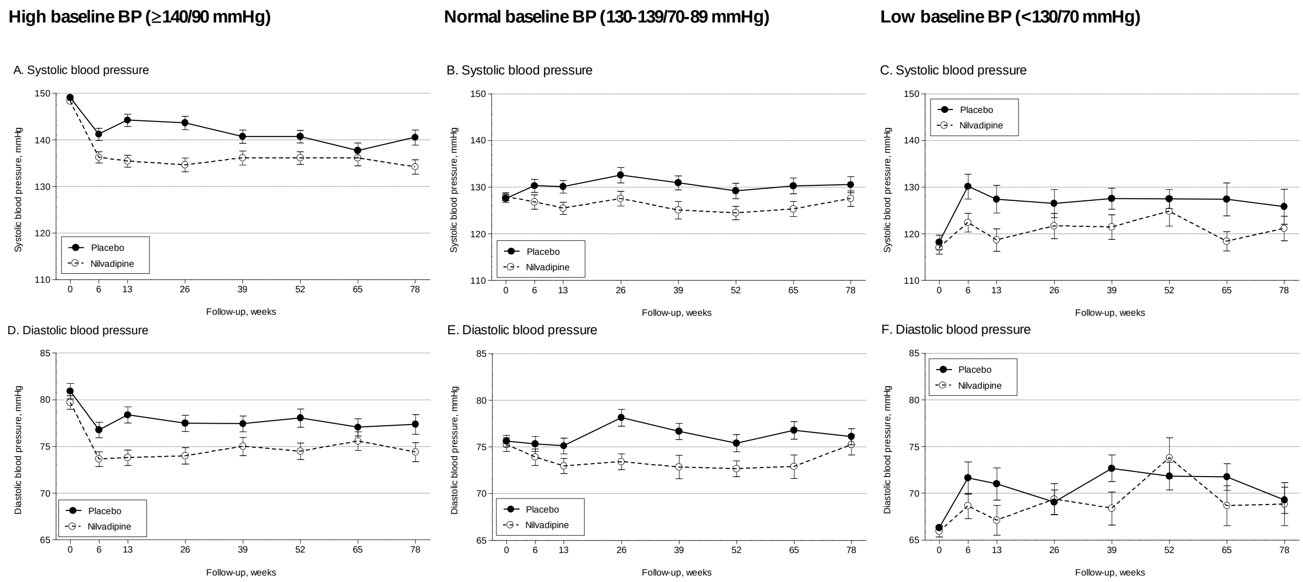
Table S5. Results from regression models estimating the effect of treatment and moderators on orthostatic hypotension.

	BP status		MMSE score		Age		Frailty Index	
Parameter	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***
Classic OH								
Treatment	0.52 (0.37)	0.16	1.58 (0.91)	0.08	0.07 (0.16)	0.68	-0.05 (0.37)	0.89
Moderator	0.04 (0.18)	0.82	0.03 (0.03)	0.37	0.01 (0.02)	0.47	0.98 (1.12)	0.38
Interaction	-0.30 (0.24)	0.19	-0.07 (0.04)	0.09	0.00 (0.02)	0.87	0.75 (1.52)	0.62
Sit-stand OH								
Treatment	0.26 (0.29)	0.38	1.23 (0.71)	0.09	-0.33 (113)	0.77	0.20 (0.13)	0.13
Moderator	-0.01 (0.14)	0.95	0.03 (0.03)	0.18	0.00 (0.01)	0.97	0.27 (0.92)	0.77
Interaction	-0.05 (0.19)	0.78	-0.05 (0.03)	0.14	0.01 (0.02)	0.65	1.15 (1.24)	0.36
ΔSBP (mmHg)								
Treatment	-1.47(1.13)	0.20	-3.47 (2.64)	0.19	-4.67 (4.36)	0.29	-0.74 (0.49)	0.14
Moderator	0.28 (0.51)	0.58	-0.04 (0.09)	0.66	-0.02 (0.05)	0.69	-0.67 (3.31)	0.84
Interaction	0.49 (0.72)	0.50	0.14 (0.13)	0.29	0.05 (0.06)	0.37	0.99 (4.70)	0.83
ΔSBP (%)								
Treatment	-1.25 (0.86)	0.15	-2.48 (2.02)	0.22	-3.90 (3.34)	0.24	-0.58 (0.37)	0.12
Moderator	0.22 (0.39)	0.57	-0.02 (0.07)	0.73	-0.02 (0.03)	0.63	-0.56 (2.52)	0.82
Interaction	0.45 (0.55)	0.41	0.10 (0.10)	0.33	0.05 (0.05)	0.32	1.25 (3.58)	0.73
	Diabetes		**Additional antihypertensive**		**Antidepressant**		**Cholinesterase inhibitor**	
Parameter	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***
Classic OH								
Treatment	0.09 (0.16)	0.60	0.11 (0.19)	0.56	0.10 (0.20)	0.60	0.14 (0.43)	0.74
Moderator	-0.04 (0.65)	0.95	-0.02 (0.24)	0.93	0.11 (0.25)	0.66	-0.34 (0.35)	0.32
Interaction	-0.05 (0.75)	0.95	-0.12 (0.35)	0.73	-0.07 (0.33)	0.83	-0.08 (0.46)	0.86
Sit-stand OH								
Treatment	0.17 (0.13)	0.18	0.07 (0.15)	0.63	0.15 (0.16)	0.35	0.31 (0.37)	0.41
Moderator	-0.13 (0.53)	0.81	-0.39 (0.20)	0.05	0.23 (0.20)	0.25	-0.01 (0.30)	0.98
Interaction	0.17 (0.60)	0.78	0.30 (0.28)	0.27	0.07 (0.26)	0.78	-0.15 (0.40)	0.71
ΔSBP (mmHg)								
Treatment	-0.90 (0.51)	0.08	-0.98 (0.61)	0.11	-0.67 (0.61)	0.27	-2.36 (1.45)	0.10
Moderator	0.17 (1.95)	0.09	0.36 (0.72)	0.62	-0.32 (0.74)	0.67	0.55 (1.13)	0.62
Interaction	1.26 (2.24)	0.57	0.71 (1.03)	0.49	-0.21 (1.01)	0.83	1.84 (1.54)	0.23
ΔSBP (%)								
Treatment	-0.69 (0.39)	0.08	-0.75 (0.47)	0.11	-0.49 (0.47)	0.30	-1.77 (1.11)	0.11
Moderator	0.12 (1.50)	0.94	0.32 (0.55)	0.57	-0.26 (0.57)	0.65	0.33 (0.87)	0.70
Interaction	0.90 (1.72)	0.60	0.53 (0.79)	0.50	-0.24 (0.78)	0.76	1.37 (1.18)	0.25

Results from logistic regression models (classic OH, sit-stand OH) or linear regression models (ΔSBP), with random intercepts for patient and study site, fixed effects for treatment, baseline ΔSBP and moderator and the interaction term for treatment*moderator. Definitions: classic OH=drop of ≥20 mmHg in systolic BP or ≥10 mmHg in diastolic BP after 1 minute. Sit-stand OH=drop of ≥15 mmHg in systolic BP or ≥7 mmHg in diastolic BP after 1 minute. ΔSBP=change in systolic blood pressure from sitting to standing expressed in mmHg and in % from sitting systolic blood pressure. BP status=high (≥140/90 mmHg), normal (130-139/70-89 mmHg) or low (<130/70 mmHg) blood pressure at baseline.

OH, orthostatic hypotension; SBP, systolic blood pressure; MMSE, Mini-Mental State Examination; AHD, antihypertensive drug; ΔSBP, change in systolic BP from sitting to standing.

Figure S1. Effect of treatment on sitting systolic and diastolic blood pressure in patients with high, normal and low blood pressure at baseline



No. of patients

	0	6	13	26	39	52	65	78
Placebo	118	115	113	112	106	98	96	94
Nilvadipine	137	132	130	126	114	111	106	100

No. of patients

	0	6	13	26	39	52	65	78
Placebo	93	90	90	84	82	75	73	73
Nilvadipine	76	75	75	71	68	64	62	62

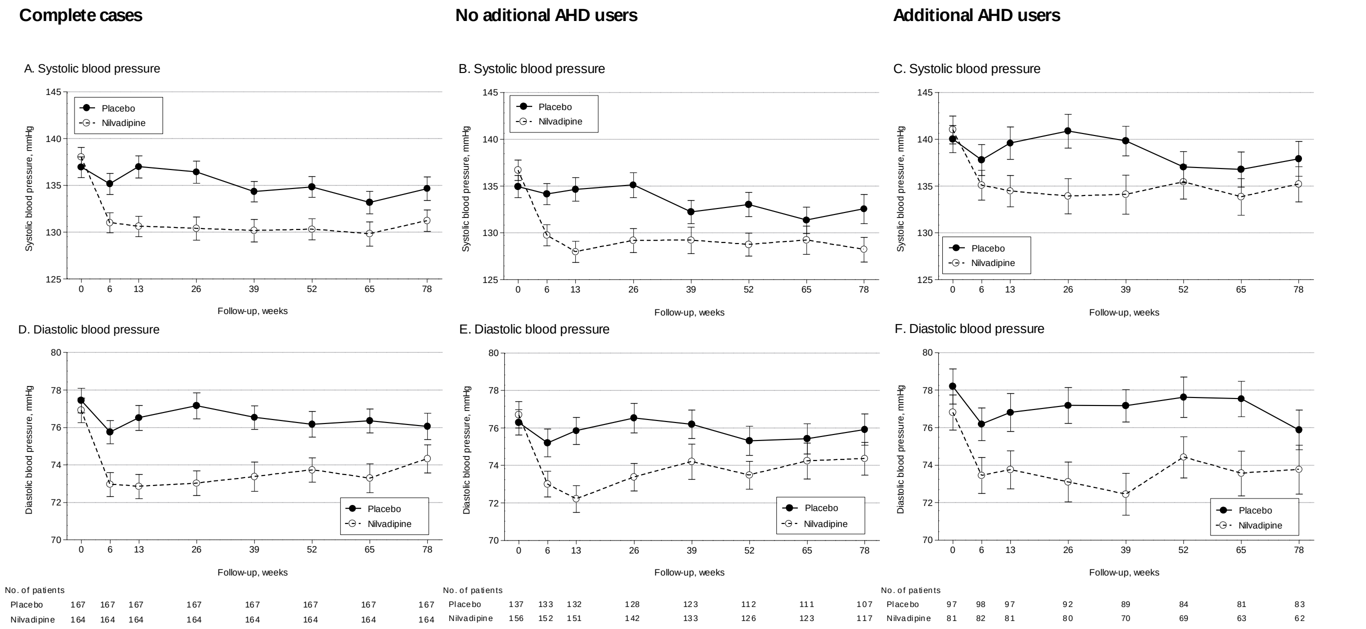
No. of patients

	0	6	13	26	39	52	65	78
Placebo	26	26	26	24	24	23	23	23
Nilvadipine	27	27	27	25	21	20	18	17

Mean sitting systolic (A, B, C) and diastolic (E, F, G) blood pressure per visit in patients with high (≥140/90 mmHg), normal (130-139/70-89 mmHg) and low (<130/70 mmHg) baseline blood pressure for nilvadipine (dashed line) and placebo (solid line). After 13 weeks of treatment, mean difference between nilvadipine and placebo was -8.0/-3.5 mmHg, -4.7/-1.7 mmHg and -7.6/-3.5 mmHg for high-, normal- and low-BP, respectively. No interaction was present between treatment and baseline BP (*P*=0.45 for systolic and *P*=0.55 for diastolic blood pressure), assessed after 13 weeks. Error bars indicate standard error of mean.

BP=blood pressure.

Figure S2. Effect of treatment on sitting systolic and diastolic blood pressure for complete cases and for use of additional antihypertensive drugs parallel to the intervention.



Mean sitting systolic (A, B, C) and diastolic (E, F, G) blood pressure per visit in the complete cases (A, D) and in non-users (B, D) and users (C, F) of additional antihypertensive drugs parallel to the intervention for nilvadipine (dashed line) and placebo (solid line). After 13 weeks of treatment, mean difference between nilvadipine and placebo was -7.4/-3.1 mmHg, -8.0/-3.9 mmHg, -6.1/-1.7 mmHg for complete cases, non-users and users, respectively. No interaction was present between treatment and use of antihypertensive drugs (P=0.48 for systolic and P=0.20 for diastolic blood pressure). Error bars indicate standard error of mean. BP=blood pressure; AHD=antihypertensive drugs.