Blood pressure and neuropsychiatric symptoms in old age

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Chapter 10

General discussion

Blood pressure and cognitive and psychological dysfunction in old age

Observational evidence

Observational evidence indicates that the relationship between blood pressure (BP) and cognitive and psychological dysfunction reverses with aging.[1] A higher BP is associated with increased risk of cognitive dysfunction in persons aged <75 years, but with better cognitive function in those aged >75 years.[2] Similarly, in a depression-free cohort of persons aged >60 years that was followed for 18 years, increasing BP preceded incident depressive disorder,[3] whereas in octogenarians a declining BP during the last decade was associated with subsequent symptoms of depression.[4] In line with this evidence, we demonstrated that in older depressed participants with a mean age of 70 years, a higher BP was associated with symptoms of apathy whereas this relationship was inversed in participants with a poorer functional ability and a mean age of 81 years. Thus, a higher BP in middle age can be seen as a risk factor for cerebral damage and cognitive and psychological dysfunction, whereas in the oldest-old a higher BP may be needed to maintain an adequate cerebral blood flow and function. (figure 1)

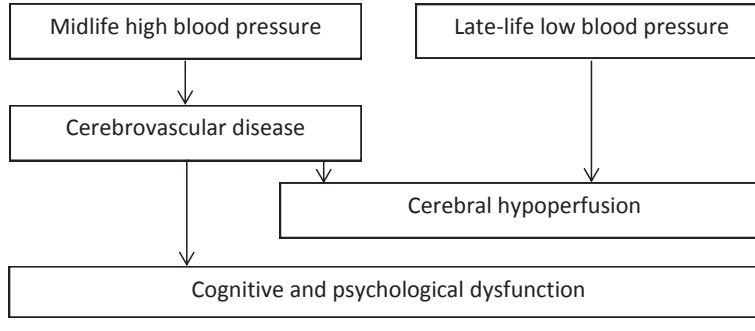

FIGURE 1. Pathways that might link midlife high blood pressure and late-life low blood pressure to cognitive and psychological dysfunction at old age.
Figure adapted from JAMA Intern Med. 2015;175:586-58745

The temporality of the relationship between a higher BP and apathy in younger elderly remains a matter of debate. As mentioned, a higher BP may induce (sub)clinical cerebrovascular disease and lead to symptoms of apathy[5;6] via disruption of the frontal-subcortical circuit.[5;7] Vice versa apathy, but not depression, has been demonstrated to independently increase the risk for a higher BP and incident cardiovascular disease, possibly through deleterious health behaviors.[8] The key symptom of apathy is diminished motivation that is expressed by diminished goal-directed behavior, cognition and emotion. Thus, apathy, by its very nature, can cause unfavorable health behaviors that increase vascular risk, such as smoking, physical inactivity and non-compliance.[9]

We demonstrated that in the oldest-old persons with poorer functional ability, a lower rather than a higher BP was associated with symptoms of apathy. In line with these findings, a lower BP in older persons with functional disabilities was earlier shown to be related to other adverse outcomes, including cognitive decline,[10] stroke,[11] and mortality.[12] These findings may be explained by the fact that a large proportion of older persons with functional disabilities have widespread vascular damage[13] and an impaired cerebral autoregulation. A lower BP may lead to cerebral hypoperfusion[14] and, thereby, to cerebral dysfunction[10] and (possibly) to cerebral damage.[11] In line with this reasoning, we found that, at old age, a lower BP was associated with cerebral grey matter microstructural damage. These findings raise questions about the desirability of intensive BP lowering at old age, particularly in vulnerable older persons with functional disabilities.

We observed a relationship between BP and apathy, but not between BP and (other) symptoms of depression. It has also been suggested that apathy, rather than (other) symptoms of depression, has a relation with vascular factors.[8;9;15;16] Apathy is not only a frequent symptom in late-life depression[7] (as well as in several other neuropsychiatric diseases) and vascular-related cognitive dysfunction,[17] but is also observed in otherwise healthy older persons.[18] Therefore, reliable instruments are needed to assess apathy, in addition to depression and cognitive dysfunction, which will allow to distinguish its differential (vascular) risk and causal factors. We showed that the Geriatric Depression Scale (GDS)-3A,[16] a three-item subset of the GDS-15 which is increasingly used as a measure for apathy in research settings[5;19] was only moderately accurate in discriminating between the presence and absence of clinically relevant apathy, as compared with the Apathy Scale. However, when no other measure for apathy is available, the GDS-3A can still be used, preferably in large studies as, under the assumption of non-differential misclassification, this may yield effect estimates biased towards the null.

Effect of discontinuation of antihypertensive treatment on cognitive and psychological functioning: trial evidence

The clinical value of the DANTE Study Leiden is modest because, in contradiction to our hypothesis, it did not demonstrate any benefits of discontinuation of antihypertensive treatment in persons aged 75 years and older with mild cognitive deficits and a systolic BP ≤160 mmHg.[20] Although the discontinuation group had a significantly greater increase in systolic BP (149-154 mmHg) than the continuation group, no differences between the groups in cognitive and psychological functioning, or in cerebral blood flow, were observed at the 4-month follow-up.[21]

Due to the lack of effect of the trial it is not possible to make any clear clinical recommendations. Nevertheless, the methodological value of the DANTE Study Leiden is considerable. The discontinuation design represents a paradigm shift in the way trials

in old age are conducted because, until now, the large majority has focused on initiation rather than on discontinuation of treatment.

Polypharmacy is common in older persons, i.e. up to 50% of persons ≥ 80 years uses ≥ 5 medications.[22] In the aging Western populations the prevalence of polypharmacy and its related problems (adverse drug reactions, drug-drug and drug-disease interactions, and non-adherence) will increase.[23] Certain, particularly vulnerable, populations may experience more harm than benefit from treatment. Therefore, there is a growing need for evidence to support recommendations for discontinuation of (antihypertensive) treatment as, currently, no such guidelines are available.

Several methodological strengths of the DANTE Study could be applied to examine the discontinuation of other chronic medications.[24] The DANTE Study used patient-relevant rather than 'hard' outcomes, i.e. we assessed cognitive, psychological and general daily functioning, rather than solely death or cardiovascular morbidity. Although hard outcomes should be measured, it is important to also include outcomes that are important to the patients themselves. For example, an older patient may value quality of life more than lengthening of life. Furthermore, in the DANTE trial actions were taken to intensively monitor any potential harms associated with discontinuation. BP was measured weekly during the 6-week discontinuation phase, and at 6, 10 and 16 weeks after randomization; moreover, antihypertensive treatment was restarted when BP exceeded safety levels. Also, an independent 'data safety monitoring board' was established which periodically evaluated the number of deaths, cardiovascular events and hospitalizations in each group and, if necessary, made recommendations for early termination of the trial. Finally, the short-term follow-up of 4 months was ethically motivated to reduce the potential long-term cardiovascular risks of discontinuation of the treatment.

The DANTE Study Leiden is the first to assess the effect of discontinuation of antihypertensive treatment on cognitive functioning, thereby precluding comparison with other trials. However, trials that focused on initiation of antihypertensive treatment demonstrated no increased, or decreased risk of antihypertensive treatment on cognitive decline at old age.[25;26] In the HYpertension in the Very Elderly Trial (HYVET) in 3845 persons aged 80 years and older with a systolic BP 160-199 mmHg, initiating antihypertensive treatment (lowering mean systolic BP from 173-143 mmHg) did not reduce incident dementia, but did reduce cardiovascular morbidity and total mortality at 2.2-year follow-up, compared to placebo.[27] The recent Systolic Blood Pressure Intervention Trial (SPRINT)[28] demonstrated that lowering systolic BP to less than 120 mmHg in 2636 community-dwelling persons aged 75 years and older[29] was beneficial in reducing fatal and nonfatal major cardiovascular events and total mortality at 3.3-year follow-up, compared to lowering systolic BP to less than 140 mmHg. The SPRINT[29] and HYVET[30] exploratory post-hoc analyses provide no evidence that functional status modified any benefits of antihypertensive treatment. These findings appear to be in contrast with

the above-mentioned observational research showing an adverse impact of a lower BP in lower-functioning older persons.[10;11] However, it is important to consider the limited generalizability of the results of the HYVET and SPRINT, because in both these trials persons with heart failure, dementia or those requiring nursing care were excluded; additionally, in SPRINT, those with a history of diabetes mellitus II or stroke, and in HYVET those with clinically relevant orthostatic hypotension, were also excluded.

Finally, the DANTE Study showed that discontinuation of all antihypertensive treatment reduces the risk of orthostatic hypotension, compared to continuation of treatment. In contrast, SPRINT[28] showed that intensive antihypertensive treatment reduces the risk of orthostatic hypotension compared to less intensive treatment. On the one hand, antihypertensive treatment may reduce the risk of orthostatic hypotension by preventing vascular damage, on the other it may increase the risk in those older persons with already impaired mechanisms involved in maintaining a stable BP upon standing, i.e. those with diminished baroreceptor reactivity and reduced vascular compliance. Then, antihypertensive treatment may further interfere with these mechanisms by blocking or inhibiting vasoconstriction, by reducing intravascular volume, or by blocking cardiac accelerations (depending on the class of antihypertensive drugs).

Limitations

Several methodological limitations of the studies described in this thesis need to be addressed. Baseline data from the DANTE and NESDO Study were used to investigate the relationships between BP, symptoms of apathy and depression, and cerebral microstructural damage. First, all participants of the DANTE Study used antihypertensive treatment at baseline, so that the relation between the true 'untreated' BP and these outcomes remains elusive. Second, generalizability of our observational findings is limited because, in the DANTE Study, persons with dementia or serious cardiovascular disease were excluded (based on safety reasons), and data from older persons *with* a diagnosis of late-life depression of the NESDO Study were employed. Third, due to the observational cross-sectional design we cannot determine any temporal relations. Although we hypothesized that a lower BP might precede symptoms of apathy and of microstructural damage, this might occur in a vice versa manner. Also, despite the correction for several confounders, due to the lack of consistency and exchangeability any association found in these studies does not imply causation.[31]

A trial is considered the gold standard to determine causal relationships. Nevertheless, as already mentioned, the generalizability of the DANTE trial is compromised due to strict selection of the study population with less comorbidities and a higher functional status than average for their age, which may have led to the inadvertent selection of an older population with a relatively intact cerebral autoregulation. Furthermore, it is possible that

the short-term follow-up is a reason for the lack of any effect of the trial. However, it is unlikely that lengthening the follow-up period for the current study population (i.e. with a probably intact cerebral autoregulation) would have detected any 'delayed' effect on cerebral blood flow and functioning.

Strengths

This thesis provides additional insight into the role of late-life BP in cognitive and psychological dysfunction, which is important in view of the aging Western populations. This thesis presents both observational evidence, using baseline data of large cohort studies in older persons, and evidence emerging from a randomized clinical trial. The DANTE Study is the first trial to determine whether discontinuation of antihypertensive treatment improves cognitive and psychological functioning. A major strength of the DANTE Study is its innovative discontinuation design with intensive monitoring of the adverse effects of discontinuation of treatment and assessment of patient-related outcomes. Other strengths include the extensive assessment of cognitive and psychological functioning as well as orthostatic hypotension, the successful intervention (as intended, a significant increase in BP was attained in the intervention group), the low drop-out rate, and the high degree of data capture. Furthermore, in the MRI substudy (in a subset of participants) features of small vessel disease, cerebral blood flow and cerebral microstructural damage were broadly assessed using different MRI sequences. This allowed us to cross-sectionally investigate their relationship with BP and cognitive and psychological functioning. Moreover, we clearly demonstrated the vital role that functional ability plays in the relationship between BP and symptoms of apathy at old age, thereby underlining the need for a tailor-made approach for the determination of late-life BP targets. Finally, the extensive assessment of distinct depressive symptom domains in the NESDO study allowed us to disentangle their complex relationship with BP, indicating that particular attention should be paid to symptoms of apathy.

Implications for future studies

Future studies should investigate whether older persons with an established impaired cerebral autoregulation can benefit from discontinuation of antihypertensive treatment in relation to their cognitive and psychological functioning. To be able to identify those participants with impaired cerebral autoregulation, we recommend to assess dynamic, rather than static, cerebral autoregulation. In the MRI substudy (n=102) static cerebral autoregulation measurements were performed: using 3-tesla MRI Quantative Flow (QF) and Arterial Spin Labeling (ASL) at baseline and at 16-week follow-up, the effect of a gradual

change in BP on a steady-state change in cerebral blood flow was determined.[21] However, because cerebral blood flow measurements are known for their large measurement error, no definite conclusions can be drawn based on this relatively small sample size. Moreover, assessment of dynamic cerebral autoregulation offers the opportunity to evaluate fast changes in cerebral blood flow velocity (e.g. by using transcranial Doppler ultrasonography or cerebral MRI) in response to a rapid alteration in BP (e.g. by using a lower-body-negative-pressure-box to induce hypotension).[32] This method may help to identify those patients with impaired cerebral autoregulation. Nursing home residents could form a population of interest as they often have more serious cerebrovascular disease[33] and, therefore, are more prone to an impaired cerebral autoregulation.

Even if future research shows that, in older persons with an impaired cerebral autoregulation, discontinuation of antihypertensive treatment can improve cerebral blood flow, it remains debatable whether this may lead to a short-term effect on cognitive and psychological function. A sustained increase in cerebral blood flow during a longer period may be needed to prevent long-term structural damage (such as lacunar infarcts[34] or white matter lesions) and, thereby, prevent cognitive deterioration. Therefore, future trials should include structural cerebral MRI at baseline and long-term follow-up. Furthermore, although the incidence of cardiovascular events and deaths was similar between the groups during the 4-month follow-up, assessment of the risks of discontinuation of antihypertensive treatment requires a longer-term follow-up. Although such research would pose important ethical dilemmas, it could provide the essential knowledge for the development of clinical BP guidelines for older persons with various degrees of functional status.

Future studies might also explore the role of cardiac functioning (e.g. by performing cardiac MRI). In the DANTE Study, because individuals with heart failure were excluded and cardiac functioning was not assessed, we cannot determine to what extent cardiac dysfunction influenced our findings. The Leiden 85-plus Study showed that persons aged 85 years with the combination of a high NT-proBNP (a frequently used serum marker of heart failure) and lower BP had the steepest cognitive decline compared with all other participants.[35] This finding suggests that specifically the combination of the two is most detrimental for the maintenance of adequate cerebral blood flow and function.

Clinical recommendations

The clinical impact of the DANTE Study is modest as it addressed a narrowly defined research question, and showed no short-term beneficial effects of discontinuation of antihypertensive treatment on cognitive and psychological functioning. Therefore, to be able to offer clinical recommendations we should also consider the current guidelines.

Current guidelines provide varying recommendations for the optimal systolic BP targets in older persons. The latest 2014 USA recommendations from the eighth Joint National Committee (JNC 8) recommend less aggressive targeting of BP thresholds for older persons compared with the JNC 7, allowing a target as high as 150/90 mm Hg for persons aged 60 years or older.[36] Based on the HYVET findings, the 2013 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guideline[37] recommend for persons aged > 80 years in good physical and mental health condition, treatment initiation only in case of a systolic BP above 160 mmHg to a goal of 140-150 mmHg. Similarly, the Dutch guideline on cardiovascular risk management states that patients aged 80 years are only considered as hypertensive patients when the systolic BP exceeds 160 mmHg.[38] The majority of international guidelines recommends treating healthy persons older than 80 years with a systolic BP over 160 mmHg to between 140-150 mmHg, and avoiding a systolic BP lower than 130 mmHg.[23]

The recent SPRINT trial[28] provides evidence for beneficial effects of lower systolic BP targets (≤120 mmHg) on cardiovascular morbidity and mortality, than is currently recommended for persons aged >75 years. However, the group with a target systolic BP ≤120 mmHg had a higher rate of syncope, electrolyte abnormalities and renal failure compared to the group with a target systolic BP ≤140 mmHg. Such adverse drug reactions and interactions would be even more common in lower-functioning older persons in whom polypharmacy is a frequent problem. As lower-functioning older persons were not included in SPRINT, or in other trials upon which the BP guidelines are based, these findings may not apply to them.

The JNC 8 does not give specific recommendations for persons aged over 80 years, or for persons with varying functional abilities.[36] For lower-functioning 'frail' hypertensive patients aged ≥ 80 years, the ESH/ESC guideline recommends: *'to leave decisions about antihypertensive therapy to the treating physician and based on monitoring of the clinical effects of treatment'*.[39] After the publication of this guideline, the ESH and the European Union Geriatric Medicine Society (EUGM) created a working group with the aim to discuss a more in-depth recommendation.[40] This group recommends that a treatment decision for frail older persons should be preceded by "*(1) information on their functional capacity, cognitive status and if possible a patient's prognosis, 2) attention to polypharmacy, (3) stratification of the frailty status, (4) identification and correction of factors that predispose to an excessive BP reduction, orthostatic hypotension, and other hypotensive episodes, such as dehydration (..)".* Furthermore, monotherapy with a low drug dose should be pursued first, and a patient should be routinely monitored. In concordance, a Canadian guideline specifically developed for frailer older persons, recommends in general not to prescribe more than two antihypertensive drugs, and to start antihypertensive treatment only if systolic BP exceeds 160 mmHg (or exceeds 190 mmHg for the severely frail older persons with limited life expectancy).[41]

In conclusion, increasing observational evidence indicates that age[1] and functional status[12;42] are of pivotal importance in the relationship between BP and adverse health outcomes. Trials in lower-functioning older persons with evidence of advanced arterial stiffness are needed to provide the knowledge necessary for tailored BP guidelines in aging Western populations. Until then, the clinician needs to continue to weigh all the pros and cons of (intensive) antihypertensive treatment for each individual patient and, preferably, make a decision together with the patient as to whether or not to start, continue, or discontinue antihypertensive treatment and also to establish which target BP needs to be pursued.

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Addendum

Nederlandse samenvatting
List of publications
Curriculum Vitae
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