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High blood pressure and its treatment in the very old: balancing benefits and risks

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Chapter 1

General introduction

The term 'hard pulse disease' is found in ancient literature as early as 2600 BC,[1] but it would be another 4500 years before Nikolai Sergeyevich Korotkoff's stethoscopic sounds and Janeway's term 'hypertensive vascular disease' laid the foundations for the current definition of hypertension.[2-4] At the end of the 19th century, Frederick Akbar Mahomed demonstrated that high blood pressure not only affects the heart, kidneys, and brain but can also be present in seemingly healthy adults.[5] In addition, Mahomed was one of the first to observe the association between age and the prevalence of high blood pressure, a relationship that formed the basis for many decades of further research (including this thesis).

Although a well-described concept, until the early 1950's high blood pressure was seen as a compensatory mechanism that maintained perfusion to diseased organs; thus representing an essential process that should not be interfered with,[6] a view that likely contributed to the death of US President Franklin D. Roosevelt. Despite increasing blood pressure values of up to 300/190 mmHg in the last years of his life, Roosevelt's fatal cerebral haemorrhage, while probably not solely attributable to essential hypertension, was "unexpected" according to official sources.[6,7] A few years later, observational evidence from the famous Framingham study established high blood pressure as one of the major cardiometabolic risk factors associated with severe cardiovascular events and death;[8] a fact that had already been demonstrated on a smaller scale by the insurance industry.[9]

Nonetheless, it wasn't until 1967 that the Journal of the American Medical Association published the results of the first trial showing the beneficial effects of blood pressure lowering on the incidence of stroke, myocardial infarction and death.[10] Half a century later, and after more than 20 landmark trials,[11] the physician's therapeutic arsenal now comprises a plethora of antihypertensive drugs. Even today hypertension is one of the most important modifiable risk factors for cardiovascular diseases and remains the most important risk factor for early death worldwide.[12]

TREATING HIGH BLOOD PRESSURE IN VERY OLD AGE: BALANCING THE BENEFITS AND RISKS

Potential benefits of treating high blood pressure in the very old

Although the first trial showing the beneficial effects of antihypertensive treatment dates back to 1967,[10] it was only in 2008 that the HYVET trial showed that lowering blood pressure by 15.0/6.1 mmHg significantly decreases the risk of death from stroke and death from any cause in those aged 80 years and older.[13] High blood pressure was once considered a mechanism best left alone,[6,14,15] especially in older adults, but this trial settled the question of whether antihypertensive treatment should be indicated in octogenarians. More recently, two trials with slightly different designs showed that antihypertensive treatment regimens in older

people, with more stricter targets for systolic blood pressure (SBP), resulted in a statistically significant reduction in cardiovascular events.[16,17] The SPRINT[16] (SBP <120 mmHg vs. <140 mmHg) and STEP[17] Trials (SBP <130 mmHg vs. <150 mmHg) both included relatively 'young' older adults, mean ages 68 and 66 years respectively, and excluded participants with a history of stroke or dementia.

However, despite the high-level evidence from these three landmark trials, the generalizability of their results to every older individual remains a controversial issue.[18-21] Since the study participants included in all three trials showed a (very) low degree of physical and/or cognitive impairment, one can question how applicable those strict targets are to the broader, heterogeneous population of older adults. Furthermore, a systematic understanding of the impact of antihypertensive treatment on the prevention of dementia is still lacking. While midlife hypertension, defined as SBP ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, is associated with an increased risk of dementia, in later life a higher SBP but lower DBP are associated with an increased risk of dementia.[22] Still, neither the SPRINT nor HYVET trial was able to show a significant reduction in the incidence of dementia.[23,24] A meta-analysis of 12 trials (mean participant age 69 years) including both SPRINT and HYVET trials, however, showed that antihypertensive treatment over an average of 4.1 years was associated with a significant reduction in the incidence of cognitive impairment or dementia.[25]

Potential risks of treating high blood pressure in the very old

Community-based longitudinal observational studies reflect a more representative sample of the aged population than the aforementioned landmark hypertension trials. Several of these observational cohort studies challenge the benefits of intensive antihypertensive treatment in older adults with cognitive and/or physical impairments.[18] Studies of multiple cohorts of older adults, originating from various countries, have shown that in these older adults, low blood pressure under antihypertensive treatment is associated with accelerated cognitive decline and increased all-cause mortality.[26-28] Although the observational nature of these studies limits the causal interpretation of their results, these findings may be related to physiological changes at advanced age. These changes include arterial wall stiffening leading to increased SBP and decreased DBP, a reduced baroreflex sensitivity leading to postural hypotension, and overall higher drug potency due to reduced glomerular filtration.[29] Additionally, weight loss, dehydration and polypharmacy are also factors that influence blood pressure.[29] To sum up, as individuals age and develop frailty, their ability to maintain adequate blood pressure in response to stress and modulation by antihypertensive treatment could become deficient over time, potentially leading to adverse events.[18,29,30]

Knowledge gaps

Despite the high quality of available evidence regarding the effects of antihypertensive treatment in old age, translation into clinical guidance for a heterogeneous population of older adults remains challenging. While several randomised controlled trials (RCTs) have confirmed the benefits of intensive antihypertensive treatment,[13,16,17] older adults with multiple comorbidities and cognitive impairment were frequently excluded from these trials. Population-based observational cohort studies have shown that low blood pressure under antihypertensive treatment, especially in these trial-excluded subgroups, is associated with negative outcomes.[26-28] Moreover, frail older adults are not only at higher risk for cardiovascular events but also more susceptible to severe side effects of antihypertensive treatment, leading to an unclear benefit-risk balance.[31,32] The intensity and thereby numerical target of antihypertensive treatment aims for a balance between cardiovascular risk reduction and the chance of side effects. While strict treatment of high blood pressure in middle-aged and robust older adults is an important tool for the preservation of cardiovascular and overall health, less intensive blood pressure management could be an acceptable strategy to maintain quality of life, particularly in the latter stages of life. To date, no large RCT has been conducted that provides sufficiently clear evidence to define the optimal intensity of antihypertensive treatment in the frail older population.

DEPRESCRIBING ANTIHYPERTENSIVE TREATMENT IN VERY OLD AGE

The rationale behind deprescribing in the presence of cognitive and physical impairments

When more drugs are prescribed than indicated, the chance of adverse outcomes increases and the therapeutic aim misses its target. Since the combined processes of ageing, multimorbidity and polypharmacy itself impact pharmacokinetic and dynamic responses,[29,33] the question inevitably arises whether the deprescribing of certain drugs becomes a therapeutic option in older adults with multimorbidity. Especially in the very old, preventive rather than symptomatic drugs are a more appropriate option for deprescribing.[34]

In the context of the prevention of cardiovascular diseases, antihypertensive treatment is both frequently prescribed in frail older adults and is linked to potentially severe side effects,[34-36] making it an interesting target for deprescribing. In contrast to abundant trial evidence on starting and intensifying antihypertensive treatment, interventional studies testing the concept of deprescribing antihypertensive treatment remain relatively scarce.[37] The Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) Study investigated whether temporary discontinuation of antihypertensive treatment

improves cognitive, psychological and general daily functioning in community-dwelling persons 75 years or older with mild cognitive impairment.[38] Although this trial concluded that discontinuation of antihypertensive treatment had no beneficial effect, it was not associated with any harm. The OPTIMISE trial,[39] including adults aged 80 years and older with a baseline SBP <150 mmHg, showed that deprescribing antihypertensive treatment was non-inferior compared with usual care, and found no statistically significant effects on quality of life or the incidence of serious adverse events. The small number of published RCTs on the deprescribing of antihypertensive treatment in older adults suggests that it is an acceptable strategy with no direct harm.[37] However, the described studies only had a relatively short follow-up. Consequently, the evidence guiding current strategies on deprescribing antihypertensive treatment is mainly based on observational associations, trials without long-term follow-up and expert opinion.[36] This compels physicians to consider the option of deprescribing predominantly based on clinical judgement.

Deprescribing antihypertensive treatment in nursing home residents with dementia

Previous research has shown that dementia is associated with a preceding drop in SBP.[40] In addition, antihypertensive treatment in concomitant dementia could produce additional side effects, such as hypotension, falls and increased anticholinergic burden.[41,42] Moreover, observational studies suggest that antihypertensive treatment increases the risk for so-called neuropsychiatric symptoms,[43,44] otherwise known as the behavioural and psychological symptoms of dementia. These core features of dementia have a major impact on quality of life.[45] Since the harms of antihypertensive treatment may outweigh the benefits when life expectancy is limited, older adults with moderate-to-severe dementia residing in a long-term care nursing home could potentially derive the greatest benefit from deprescribing antihypertensive treatment.[18,41] However, currently available evidence on the deprescribing of antihypertensive treatment originates from trials among community-dwelling older adults without dementia,[37] and no RCT assessing the benefit-harm balance of deprescribing antihypertensive treatment in older individuals with dementia nor in those residing in long-term care has been published to date. While intensive antihypertensive treatment is a factor in the prevention of physical and (potentially) cognitive decline in robust older adults, a permissive higher blood pressure by deprescribing antihypertensive treatment could be a promising approach in older nursing home residents with dementia. Not only to decrease neuropsychiatric symptoms but also to maintain quality of life in this vulnerable population.

Although an RCT would provide more insights into the potential benefits of deprescribing antihypertensive treatment in nursing home residents with dementia, these studies are time-consuming and resource-intensive. Besides the well-known

budgetary and ethical difficulties,[46] (trial) research in the nursing home setting is complicated by the fact that the participant-researcher dyad is affected by additional stakeholders, including facility administrators, attending physicians, nursing home staff and family caregivers.[46,47] Additionally, the unfamiliarity with research, the high turnover of staff and informed consent by proxy in the presence of significant cognitive impairment all contribute to making an RCT in the nursing home setting a major challenge.[46-49]

OVERALL AIM AND OUTLINE OF THIS THESIS

The overall aim of this thesis is to investigate the benefits and risks of high blood pressure and its treatment in the very old, including whether an elevation in blood pressure by discontinuing antihypertensive treatment has any beneficial effects on older adults with physical and cognitive impairments.

We will address the following research questions:

1. *Which thresholds and targets of antihypertensive drug treatment do clinical practice guidelines on hypertension recommend in older adults and do they differ between countries?*
2. *Does individual variation between octogenarians, characterized by antihypertensive treatment, history of cardiovascular diseases, and cognitive and physical fitness, affect the associations between SBP and health outcomes such as mortality, cognition and functional status?*
3. *Does the discontinuation of antihypertensive treatment reduce neuropsychiatric symptoms and help to maintain quality of life in older nursing home residents with moderate-to-severe dementia?*
4. *Which factors play a role in decision-making on behalf of patients with dementia to participate in an RCT involving a clinical intervention such as the discontinuation of antihypertensive treatment?*

Translation of available evidence on antihypertensive treatment into clinical decision-making for a heterogeneous population of older adults is challenging. Contributing to the current debate, in **Chapter 2** we provide a systematic overview of the thresholds and targets of antihypertensive treatment in older adults recommended in current (inter)national guidelines. Additionally, we analysed potential relationships between recommended targets and guideline characteristics such as methodological quality, geographic region, intended users and the selection of underlying evidence.

As the treatment of high blood pressure in the very old remains a much-disputed subject, an essential question is how SBP and overall health outcomes are related in various subgroups of the very old. Therefore, in **Chapter 3** we combined individual participant data from the Towards Understanding Longitudinal International

older People Studies (TULIPS) consortium to investigate how individual variation in octogenarians affects the associations between SBP and outcomes including mortality, cognition and functional status. In this individual participant data meta-analysis, we characterized the variation between individuals regarding antihypertensive treatment, history of cardiovascular diseases, and cognitive and physical fitness.

While intensive antihypertensive treatment has beneficial effects on robust older adults, the harms of these drugs may outweigh the benefits in older adults with physical and cognitive impairments. We therefore conducted the DANTON study, the results of which are described in **Chapter 4**. In this RCT, we investigated the effects of the discontinuation of antihypertensive treatment on neuropsychiatric symptoms and quality of life in older nursing home residents with moderate-to-severe dementia.

Because RCTs in older adults with dementia are complicated by informed consent by proxy, we investigated how proxy decision-making concerning participation in a clinical trial unfolds in real life. Concerning participation in the DANTON study, in **Chapter 5** we further describe a qualitative analysis of the factors that played a role in decision-making by legal guardians of potential trial subjects.

In Chapter 6, we present a general discussion of the main results of individual studies in light of current literature. By answering three overarching questions, we substantiate the implications of these studies for clinical practice and further research.

REFERENCES

1. Ruskin A. Classis in Arterial Hypertension. Charles C. Thomas. Springfield:, 1956.
2. Esunge PM. From blood pressure to hypertension: the history of research. J R Soc Med. 1991; 84:621-621.
3. Janeway TC. A clinical study of hypertensive cardiovascular disease. Arch Intern Med. 1913; XII:755-798.
4. Korotkoff NS. A contribution to the problem of methods for the determination of the blood pressure. Rep Imperial Milit-Med Acad St Petersburg. 1905; 11:365.
5. Cameron JS, Hicks J. Frederick Akbar Mahomed and his role in the description of hypertension at Guy's Hospital. Kidney Int. 1996; 49:1488-1506.
6. Lüscher TF. What is a normal blood pressure? Eur Heart J. 2018; 39:2233-2240.
7. Messerli FH. This day 50 years ago. N Engl J Med. 1995; 332:1038-1039.
8. Dawber TR, Moore FE, Mann GV. Coronary heart disease in the Framingham study. Am J Public Health Nations Health. 1957; 47:4-24.
9. Blood Pressure Study, 1939. The Actuarial Society of America and the Association of Life Insurance Medical Directors. New York, NY: 1940.
10. Veterans Administration Cooperative Study Group on Anti-hypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967; 202:1028-1034.
11. Saklayen MG, Deshpande NV. Timeline of history of hypertension treatment. Front Cardiovasc Med. 2016; 3:3.
12. Global report on hypertension: the race against a silent killer. Geneva: World Health Organization; 2023.
13. Beckett NS, Peters R, Fletcher AE et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008; 358:1887-1898.
14. Kotchen TA. Historical trends and milestones in hypertension research: a model of the process of translational research. Hypertension. 2011; 58:522-538.
15. Moser M. Historical perspectives on the management of hypertension. J Clin Hypertens. 2006; 8(8 Suppl 2):15-20; quiz 39.
16. Wright JT, Jr., Williamson JD, Whelton PK et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015; 373:2103-2116.
17. Zhang W, Zhang S, Deng Y et al. Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. N Engl J Med. 2021; 385:1268-1279.
18. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. Circ Res. 2019; 124:1045-1060.
19. Jacobs JM, Stessman J, Ein-Mor E et al. Hypertension and 5-year mortality among 85-year-olds: the Jerusalem Longitudinal Study. J Am Med Dir Assoc. 2012; 13:759.e751-756.
20. Sheppard JP, Lown M, Burt J et al. Generalizability of Blood Pressure Lowering Trials to Older Patients: Cross-Sectional Analysis. J Am Geriatr Soc. 2020; 68:2508-2515.
21. Supiano MA, Williamson JD. Applying the Systolic Blood Pressure Intervention Trial Results to Older Adults. J Am Geriatr Soc. 2017; 65:16-21.
22. Ou YN, Tan CC, Shen XN et al. Blood Pressure and Risks of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of 209 Prospective Studies. Hypertension. 2020; 76:217-225.
23. Peters R, Beckett N, Forette F et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008; 7:683-689.

24. Williamson JD, Pajewski NM, Auchus AP et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA. 2019; 321:553-561.
25. Hughes D, Judge C, Murphy R et al. Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis. JAMA. 2020; 323:1934-1944.
26. Benetos A, Labat C, Rossignol P et al. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. JAMA Intern Med. 2015; 175:989-995.
27. Mossello E, Pieraccioli M, Nesti N et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015; 175:578-585.
28. Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old. Data from the Leiden 85-plus Study. Age Ageing. 2018; 47:545-550.
29. Shantsila E, Lip GYH, Shantsila A et al. Antihypertensive treatment in people of very old age with frailty: time for a paradigm shift? J Hypertens. 2023; 41:1502-1510.
30. Reeve E, Gnjidic D, Langford AV, Hilmer SN. Deprescribing antihypertensive drugs in frail older adults. Aust Prescr. 2024; 47:85-90.
31. Anker D, Santos-Eggimann B, Santschi V et al. Screening and treatment of hypertension in older adults: less is more? Public Health Rev. 2018; 39:26.
32. Veronese N, Sigeirsdottir K, Eiriksdottir G et al. Frailty and Risk of Cardiovascular Diseases in Older Persons: The Age, Gene/Environment Susceptibility-Reykjavik Study. Rejuvenation Res. 2017; 20:517-524.
33. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004; 57:6-14.
34. Sheppard JP, Benetos A, Bogaerts JMK et al. Strategies for Identifying Patients for Deprescribing of Blood Pressure Medications in Routine Practice: An Evidence Review. Curr Hypertens Rep. 2024 May;26(5):225-236.
35. Kraut R, Lundby C, Babenko O et al. Antihypertensive medication in frail older adults: A narrative review through a deprescribing lens. Am Heart J Plus. 2022; 17:100166.
36. Rivasi G, Tortù V, D'Andria MF et al. Hypertension management in frail older adults: a gap in evidence. J Hypertens. 2021; 39:400-407.
37. Reeve E, Jordan V, Thompson W et al. Withdrawal of antihypertensive drugs in older people. Cochrane Database Syst Rev. 2020; 6: Cd012572.
38. Moonen JE, Foster-Dingley JC, de Ruijter W et al. 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.
39. Sheppard JP, Burt J, Lown M et al. Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients With Hypertension Aged 80 Years and Older: The OPTIMISE Randomized Clinical Trial. JAMA. 2020; 323:2039-2051.
40. Skoog I, Lernfelt B, Landahl S et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996; 347:1141-1145.
41. Harrison JK, Van Der Wardt V, Conroy SP et al. New horizons: the management of hypertension in people with dementia. Age Ageing. 2016; 45:740-746.
42. van der Wardt V, Burton JK, Conroy S et al. Withdrawal of antihypertensive therapy in people with dementia: feasibility study. Pilot Feasibility Stud. 2018; 4:29.
43. Bassiony MM, Steinberg MS, Warren A et al. Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. Int J Geriatr Psychiatry. 2000; 15:99-107.
44. Steinberg M, Hess K, Corcoran C et al. Vascular risk factors and neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. Int J Geriatr Psychiatry. 2014; 29:153-159.

45. Shin IS, Carter M, Masterman D et al. Neuropsychiatric symptoms and quality of life in Alzheimer disease. Am J Geriatr Psychiatry. 2005; 13:469-474.
46. Lam HR, Chow S, Taylor K et al. Challenges of conducting research in long-term care facilities: a systematic review. BMC Geriatr. 2018; 18:242.
47. Shepherd V, Nuttall J, Hood K, Butler CC. Setting up a clinical trial in care homes: challenges encountered and recommendations for future research practice. BMC Res Notes. 2015; 8:306.
48. Brandt DK, Hind JA, Robbins J et al. Challenges in the design and conduct of a randomized study of two interventions for liquid aspiration. Clin Trials. 2006; 3:457-468.
49. Murfield J, Cooke M, Moyle W et al. Conducting randomized controlled trials with older people with dementia in long-term care: Challenges and lessons learnt. Int J Nurs Pract. 2011; 17:52-59.