Perspectives on treating hypertension in old age : the burden of polypharmacy, risks of treatment and GPs' treatment probability

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Summary

Physicians face a clinical dilemma when deciding on the optimal systolic blood pressure (SBP) target in old age especially in >75-year-olds, a population characterized by wide variation of cognitive and physical function. Some are very healthy, others have co-existing chronic conditions (i.e. multimorbidity) are therefore under treatment with multiple drugs (i.e. polypharmacy) or are frail.

With increasing age, blood pressure rises as a consequence of arterial stiffness and it has been debated whether or not to it is beneficial to treat hypertension in old age especially in >75-year-olds when they have multimorbidity, polypharmacy or frailty. Large hypertension trials showed that lowering SBP in >60-year-olds is beneficial and lowers the risk for myocardial infarction, stroke and all-cause mortality, even in >80-year-olds. However, these trials lack generalizability and typically excluded multimorbid patients that are frail. At the same time, observational studies rose concerns about lowering SBP too much since there are several cohort studies showing a reverse association of low SBP and increased mortality and accelerated cognitive decline especially in >75-year-olds. However, current hypertension guidelines advise physicians to lower SBP to values of even <130mmHg in all patients from the age of 60 years, which fuelled the discussions about the benefits and harms of lowering SBP too much in >75-year-olds under antihypertensive treatment especially when they are frail defined as having low hand grip strength or complex health problems in multiple domains of daily living.

This dilemma is summarized in **Chapter 1** in a case report of Mrs S, a frail 90-year-old with multimorbidity and polypharmacy, that came to her general practitioner (GP) for a routine check of her blood pressure: her SBP was 154 mmHg under antihypertensive treatment. A GP would want to protect Mrs S by treatment from stroke or myocardial infarction, and preserving her cognitive function, daily functioning and quality of life (QoL) at the same time. Mrs S represents these individuals that are often excluded from hypertension trials, thus we cannot be sure that results from such trials apply to Mrs S.

The general aim of this thesis is to increase the scientific knowledge about the effects of treating hypertension in >75-year-olds with frailty. This thesis has three aims: 1) to measure the prevalence of polypharmacy in older patients; 2) to test for an association between low SBP and mortality, cognitive function, daily functioning, and QoL in older patients under antihypertensive treatment; and 3) to understand the role that frailty plays in GP decisions about treating hypertension in old age across countries and see if those differences can be explained by country-specific cardiovascular disease burden and life expectancy.

Polypharmacy – Part of preventive cardiovascular medication

Most chronic conditions are addressed by guidelines that focus on a single disease. GPs must rely on these guidelines to treat patients with multiple chronic conditions, but when patients

have multimorbidity, single-disease guidelines can increase the prevalence of polypharmacy and potentially inappropriate polypharmacy (PIP). Still little is known on prevalence and drivers of polypharmacy.

In **Chapter 2**, we set out to measure the prevalence of polypharmacy in a random sample of 1,002 patients in Switzerland, 50 to 80 years old, in university primary care settings. We further wanted to assess the association of polypharmacy with specific comorbidities, including cardiovascular prevention, to identify subgroups of patients at higher risk of polypharmacy.

We found a high prevalence of polypharmacy: In the total age group (50-80 years), about 40% had polypharmacy, in the oldest age group (75-80), even more than half, some of them even taking 10 or more long-term medication. Patients in the oldest age-group with hypertension had an about 9-fold risk of having polypharmacy.

This study underlines the importance of reconsidering each prescription. Age and number of chronic conditions are key factors, and so is the type of disease (e.g. hypertension). GPs must both make a sound clinical judgment, and then work with their patient to determine which prescriptions should be started, continued or deprescribed, in a shared decision-making process.

Low SBP associated with mortality and cognitive decline in frail older patients with complex health problems

Observational studies that follow the population of older and frail patients with multimorbidity and polypharmacy have found that low SBP is associated with cognitive decline. Some speculate that low blood pressure due to intense antihypertensive treatment disturbs the hemodynamic regulation of the heart and brain and reduces cognitive function. A landmark study found that, in a select sample of 80-year-olds with dementia or mild cognitive impairment, low SBP was associated with worse cognitive function in patients under antihypertensive treatment but not in those without antihypertensive treatment. These findings were limited by the study's small sample size and short follow-up period of less than one year.

In **Chapters 3 and 4**, we therefore tested for an association between SBP and mortality, cognitive function, daily functioning, and QoL in older patients under antihypertensive treatment and stratified our analyses on frailty.

In **Chapter 3**, we analysed data from the Leiden 85-plus Study, a population-based prospective cohort study of 85-year-olds inhabitants of Leiden were invited (n=599). We found low SBP under antihypertensive treatment was associated with increased all-cause mortality and accelerated annual cognitive decline. But frailty, measured by hand grip strength, modified the

association with cognitive function in ways that in those with a weak hand grip strength, there was cognitive decline. In non-frail participants and in those not treated for hypertension, we found no relationship between SBP and mortality/cognitive function.

In ISCOPE, a more recent observational cohort study (n=1,266) of >75-year-olds with a one-year follow-up described in **Chapter 4**, we could confirm the same associations of low SBP with cognitive decline without any negative effect on daily functioning and QoL in participants under antihypertensive treatment. Again, the association was modified by frailty defined as having complex health problems in ways that participants with complex health problems showed an association of low SBP and cognitive decline, but not in those without. In line with the findings in the Leiden 85-plus Study, those not under antihypertensive treatment showed no evidence for the same negative association of low SBP and cognitive decline.

Since we showed that higher blood pressure under treatment is better for cognitive function and mortality, this encourages physicians to take an individualized approach when treating hypertension in >75-year-olds with frailty. We urge researchers to conduct new randomized trials to test the long-term effectiveness and safety of deprescribing antihypertensive therapy to raise SBP especially in >75-year-olds with frailty.

Variation in antihypertensive treatment in old age, according to GPs

Since evidence on optimal antihypertensive treatment in >75-year-olds with frailty is scarce and present data are conflicting, we hypothesised there could be treatment differences between physicians. In **Chapters 5 and 6**, we sought to understand the role that frailty plays in GP decisions about treating hypertension in >75-year-olds across countries and see if those differences could be explained by country-specific cardiovascular disease burden and life expectancy.

The study surveyed 2,543 GPs from 29 countries in Europe, Brazil, Israel, and New Zealand. We constructed case-vignettes, all aged >80 years like Mrs S, and found in **Chapter 5** that GPs from different countries made very different decisions about advising treatment of hypertension in these patients. Treatment advise rate ranged from 34% to 88% per country. As we hypothesized, frailty played an important role in a GPs decision to start antihypertensive treatment. In **Chapter 6**, we studied the differences between countries by specific health data about countries including CVD burden and life-expectancy at age 60. In countries with a high CVD burden, GPs were more likely to advise starting treatment of hypertension in old age. The association was modified by country-specific life expectancy at age 60. Though there was a positive association for GPs in countries with low life expectancy at age 60 years, we found no association for GPs in countries with high life expectancy at 60 years.

Both findings confirmed the hypothesis that GPs do not uniformly treat hypertension in old age, and that patient characteristics as well as national burden of CVD and life expectancy play a role in their decision, in ways like in the case of Mrs S. Both studies have several implications for research and clinical practice. High-quality cohort studies or (ideally) new hypertension trials that deliberately include frail patients are needed to gather evidence about frailty as factor in treating hypertension in >75-year-olds. Future studies should see if treatment variation can be explained by, e.g., guideline recommendations followed by individual GPs. Qualitative studies could help us better understand the variation we have identified.

Chapter 7 summarizes the main findings that 1) polypharmacy is highly prevalent in older people and hypertension is a driver for polypharmacy. 2) We found low SBP under antihypertensive treatment to be associated with increased all-cause mortality and cognitive decline in participants that were frail. 3) As hypothesised, we saw a large variation in how GPs across 29 mainly European countries decide to start antihypertensive treatment in older patients. GPs less often treated frail patients but their decision was also influenced by how large CVD burden was in their countries especially in countries with a low life expectancy.

These findings are discussed in the context of current literature and the case of Mrs S. Methodological limitations are addressed, including the main limitations of association versus causation, reverse causality and confounding. This thesis has strong implications. As directions for future research, we encourage researchers to conduct new trials to test the effectiveness and safety of stopping or reducing antihypertensive treatment (i.e. deprescribing) to increase SBP in >75-year-olds with frailty. From a clinical perspective, the findings and results of this thesis suggest we move cautiously to re-define individualized SBP thresholds in those older people under antihypertensive treatment that are frail.