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

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General introduction

Better health care and advances in prevention and treatment of diseases are some of the most important reasons that led to increased health, life-expectancy, and quality of life (QoL) of the population of >75-year-olds. But much of what we know about the risks and benefits of prevention and treatment is based on evidence from trials that usually exclude these patients. Most of those excluded have multimorbidity (two and more chronic diseases), polypharmacy (5 or more medication daily) or are frail. Frailty as a concept lacks of a standardized way to measure, but there is consensus that physical measurements e.g. hand grip strength or measures of multiple components that reflect more the impact on daily living (i.e. complex health problems) both constitute to frailty [1]. Due to the exclusion of these patients from trials, this dearth of evidence puts general practitioners (GPs) and other physicians in a difficult situation when deciding what treatments are best in old age.

GPs and their older patients must make a number of decisions, including prioritizing health care to meet patient needs, choosing the best preventive strategies for cardiovascular disease (CVD), and accounting for multimorbidity and polypharmacy. Cardiovascular prevention can serve as a typical example of the dilemmas that GPs face. Since the American Heart Association (AHA) recently updated its hypertension guidelines [2], and reduced blood pressure target values from 140 to <130 mmHg also for older patients, there has been heated debate [3]. These new treatment goals for hypertension had an immediate and dramatic effect on the general population. In the US, for example, the population in need of antihypertensive treatment jumped sharply from 32% to 46% [4].

MRS S WANTS TO KNOW HER IDEAL SYSTOLIC BLOOD PRESSURE

Figure 1. Portrait of Mrs S (symbolic)

Mrs S, a 90-year-old woman, is the kind of patient that GPs often see (Figure 1). She enters the examination room slowly, relying on her walker. She has multimorbidity and polypharmacy as she is taking eight medications including antihypertensives. A myocardial infarction a few years ago left her too frail to undergo surgery to relieve her lumbar spinal stenosis; this is why she uses a walker and is in constant pain, which limits her activities in daily life. Measured in the office, her systolic blood pressure (SBP) under treatment is 154 mmHg. Earlier measurements taken at home were between 145 and 150 mmHg. Mrs S asks her GP if he is satisfied with her current blood pressure measurement. Then, the GP starts thinking. What would be her ideal blood pressure? And how do we make that determination?

Mrs S is a typical older patient, who would almost certainly have been excluded from the hypertension trials that provide evidence for appropriate treatment. The CVD prevention guidelines that depend on the results of those trials are not based on data about patients like her. When thinking about her optimal blood pressure, it is unsure what will happen if current guidelines would be strictly followed, which suggest lowering her SBP to <150 mmHg, or even <130 mmHg. Would she benefit from a lower cardiovascular risk? Would lowering her blood pressure make her tired or dizzy and lower her QoL, or increase her risk of falling or even dying? Would she suffer from a decline in cognitive function or daily functioning?

CURRENT STATE OF KNOWLEDGE

This section provides background information on polypharmacy and treating hypertension in old age and summarizes what we know about the risks and benefits of treating hypertension in that population.

Polypharmacy in old age

Polypharmacy is usually defined as taking >5 long-term prescribed drugs [5-12]. The prevalence of polypharmacy in all adults has doubled in the last decades, rising from 11% in 1995 to 21% by 2010 [6]. As people age, the prevalence of polypharmacy increases dramatically (Figure 2). In Scotland, prevalence increased from 30% in those aged 60-69 years to almost 70% in those >80 years. In the Netherlands, prevalence increased to 60% [13]. We see the same trend in individuals who take 10 or more medications.

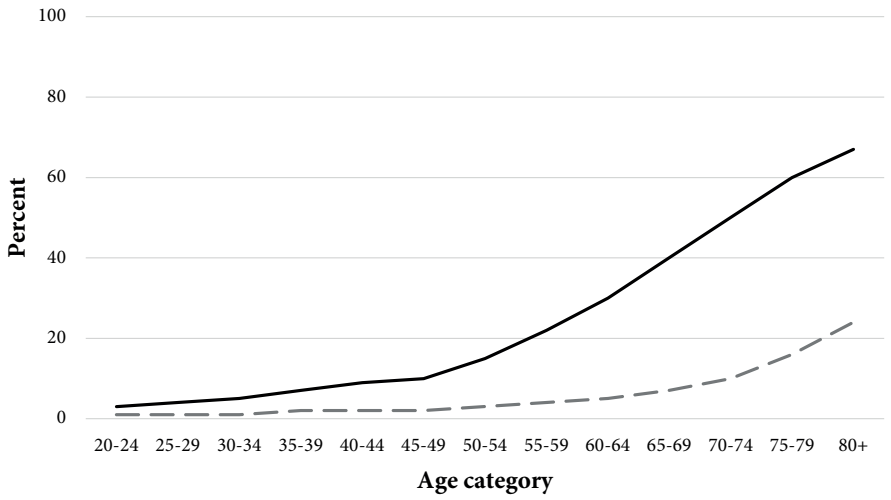

Figure 2. Increase of polypharmacy by age category. Solid line = 5 and more medications; dashed line = 10 or more medications. Adapted from [6].

Patients are likely to take more and more medication, the older they get. They, their families, GPs, and society meet the growing challenge of adapting to the increase in polypharmacy. It is therefore highly needed to determine the safety and efficacy of polypharmacy, and to find out which patients will benefit from polypharmacy and which will not. Because negative consequences of polypharmacy are well described: poor medication adherence, degraded physical and social function, worse health outcomes, higher healthcare costs, and lower QoL [11, 14, 15].

Polypharmacy has many causes. Notable among them is the tendency to address chronic conditions with disease-specific guidelines that do not take into account that a patient is multimorbid [6]. These single-disease guidelines may suggest treatment with medication without considering drug-drug and drug-disease interactions [16]. Patients who see multiple specialists may be prescribed a variety of drugs that GPs do not feel comfortable to reduce the dose or stop (also known as deprescribing) [17]. Preventive medication for CVD strongly contributes to polypharmacy, since guidelines advise that patients at increased cardiovascular risk combine blood pressure lowering medication, cholesterol lowering medication and platelet aggregation inhibitors.

Next to having different chronic conditions that attribute to polypharmacy, also treating one condition with multiple medications increases the risk to have polypharmacy. Often multiple medications are prescribed to lower blood pressure and achieve tight blood pressure control in patients with hypertension [3]. In a global cohort study [18], 16% of younger adults, with hypertension were prescribed three or more antihypertensive drugs; this rose to 38% for patients aged >75. Many of these older patients are also prescribed statins and anticoagulants, pushing them over the threshold of polypharmacy [19]. The effort to prevent CVD by lowering blood pressure with polypharmacy is also very expensive. In the UK, CVD preventive medication was the most prescribed medication in the general population, making up 30% of all prescriptions and 12% of the total primary care prescribing budget in 2016 [16].

Prevalence of hypertension in old age

In the US population, 32% have been diagnosed with hypertension (applying the threshold of SBP >140mmHg [20]. A population-based study showed prevalence of hypertension increased from about 60% in <55-year-olds to >80% in >75-year-olds (Figure 3) [21].

Longer lifespans are shifting our definitions of "old", with many more >75-year-olds and older that are the fastest-growing age group. This population will triple in the next 35 years [22], and it is very heterogeneous. Some >75-year-olds are very healthy, but many have multimorbidity and are frail. Figure 4 describes the WHO framework on ageing, adding functional capacity to the dimension of age. While functional capacity is almost equal for all in early life, a gap

in functional capacity opens in adult life and increases over the life-course. In old age, this gap crosses the disability threshold for some >75-year-olds, while others continue perform at higher levels, with little change in their capacity since early life. Though functional capacity varies widely in old age, trials and guidelines tend to treat all old people equally. However, hypertension is prevalent in >80% in old age regardless of their individual differences in functional capacity and their GPs have to decide on the optimal target blood pressure when treating hypertension [21].

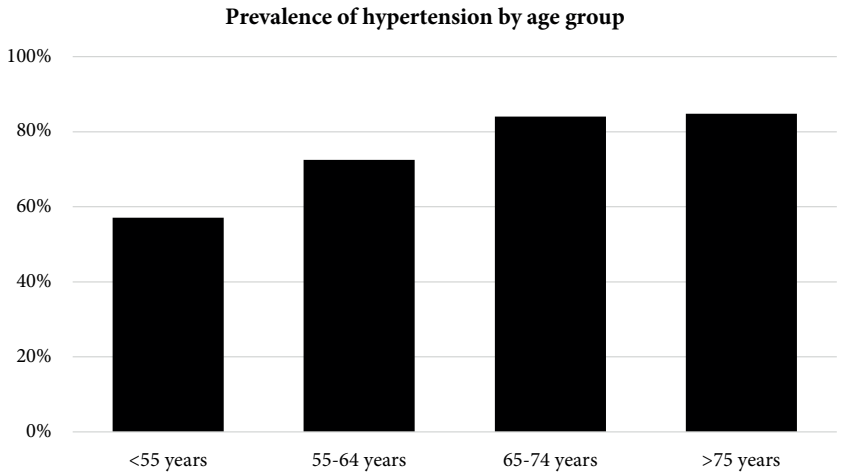

Figure 3. Percentage of hypertensive participants by age group. Adapted from [21].

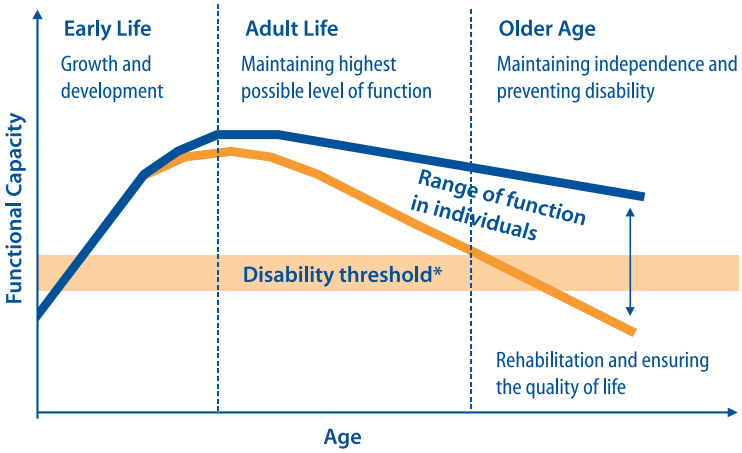

Figure 4. Heterogeneity in maintaining functional capacity over the life course [23].

Current evidence on effects of high blood pressure in old age

Hypertension is the main risk factor and preventable cause of CVD. It is responsible for many deaths from stroke, myocardial infarction, and other CVDs [24]. It injures blood vessels, so atherosclerotic plaques accumulate in the heart, brain, and other arterial beds, impairing perfusion of every major organ. When the plaques rupture, they can cause stroke and myocardial infarction. Antihypertensive treatment can prevent these injuries. However, through the 1980s this treatment was commonly withheld from old patients (>60 years) because physicians thought hypertension in old age was a healthy adaptation to arteriosclerotic rigidity [25]. In the 1990s, after trials proved that treating those over 60 for hypertension reduced stroke rates and myocardial infarction [26-28], this paradigm shifted.

We know antihypertensive treatment is effective in patients >60 years. The earliest trials, in the 1990s, studied the effect of antihypertensive treatment in >60-year-olds. The SHEP trial included almost 5,000 patients with isolated systolic hypertension (>160mmHg) and found antihypertensive treatment significantly reduced risk of stroke by 36%, and myocardial infarction by 27%. SHEP established a trend for lower mortality in the treated group [28]. Two more trials, the Swedish STOP trial [29] and the Syst-Eur trial [26], which included 23 European countries, found stroke rate and cardiovascular outcomes were similarly lower after treatment.

However, treating hypertension to prevent cardiovascular disease in >75-year-olds is still under discussion. The most influential trials on current hypertension guidelines in the past decade have been HYVET and SPRINT. In HYVET, 3,845 patients all aged >80 years were invited when their baseline SBP without antihypertensive treatment was >160mmHg. The intervention targeted an SBP of <150mmHg. HYVET found that antihypertensive treatment reduced death from any cause by 21% and a trend in reduction of stroke by 30%. In SPRINT, 9,361 non-diabetic persons with an SBP of >130mmHg and increased CVD risk were assigned to either intensive blood pressure lowering treatment (<120 mmHg) or standard treatment (<140mmHg) [30]. The primary outcome (first occurrence of myocardial infraction, stroke, acute coronary syndrome, heart failure, or CV-death) was 25% lower in the intensive-treatment group; all-cause mortality was about 30% lower. For >75-year-olds, the results were similar [31].

HYVET and SPRINT strongly suggest that treating >75-year-olds for hypertension is beneficial, but neither trial can be generalized to all patients in this age group because they excluded patients with dementia, living in nursing homes or other frail patients with multimorbidity [32]. For example, most participants in HYVET were between 80- and 85-years-old, but the median follow-up period was only 1.8 years, so HYVET did not provide much evidence about patients >85 years [33]. The only evidence for treating those over >85 years with hypertension has come from population-based cohort studies. Many of these studies raised concern

that lowering SBP too far might have negative effects like increasing mortality or accelerating cognitive decline [34-44]. However, it is challenging to draw connections between SBP and cognitive decline [45]. High SBP in midlife appears to damage cerebral vessels and impair brain function [46], but late in life, and especially in frail subjects, there is an association between low SBP and higher risk of cognitive decline [47]. If a patient already has vascular injuries, these cannot be reversed. In these patients, antihypertensive treatment may disturb hemodynamic regulation of the heart and brain, reducing cognitive function [48-53].

A landmark paper by Mosello *et al.* in 2015 found that in a cohort of cognitively impaired patients (mean age 79), lower SBP was associated with faster cognitive decline [40]. Several earlier studies made similar observations and later studies confirmed it [34-39, 43]. But Mosello *et al.* were the first to show that antihypertensive therapy modified these associations: low SBP was associated with cognitive decline only in patients being treated for hypertension. Their study was limited to patients of an outpatient memory clinic, they did not assess mortality risk and patient-related outcomes like QoL, and they did not follow up patients long enough to detect long-term protective effects of antihypertensive treatment, so they do not offer us a strong enough evidence base for developing guidelines for antihypertensive treatment in >75-year-olds.

AIM AND OUTLINE OF THIS THESIS

The general aim of this thesis is to increase the scientific knowledge about the effects of treating hypertension in >75-year-olds, especially in those 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.
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.

To address these aims, datasets from four study populations are used that include both patients and GPs. The studies were conducted in Switzerland, the Netherlands, and, in the case of the international comparative study, in 29 mainly European countries, Brazil, Israel, and New Zealand.

Polypharmacy – Part of preventive cardiovascular medication

We set out to measure the prevalence of polypharmacy in university primary care settings, to assess the association of polypharmacy with specific comorbidities, including cardiovascular prevention, and to identify subgroups of patients at higher risk of polypharmacy.

We analysed the Corif dataset, a Swiss retrospective cohort study that contains data of a random sample of 1,002 patients collected 2005-2006, from all four university primary care clinics (Basel, Geneva, Lausanne, and Zürich). Data were extracted from medical records of 50- to 80-year-old patients; of those, 67.5% had multimorbidity.

Our results are presented in **Chapter 2**.

Low SBP under antihypertensive treatment and the effect on outcomes in old age

We tested for an association between low SBP and mortality, cognitive function, daily functioning, and QoL in older patients under antihypertensive treatment. We analysed data from two cohort studies (Leiden-85 plus and ISCOPE).

The Leiden 85-plus Study is a population-based, prospective follow-up study of 599 inhabitants of the City of Leiden, the Netherlands, who turned 85 between 1997 and 1999. No selection criteria other than reaching the age of 85 years were applied. The study team visited all participants at home, at baseline, and yearly thereafter, until they turned 90. Each year, the team collected information on sociodemographic characteristics. Participants were interviewed face-to-face, and were given extensive cognitive tests, including the Mini-Mental State Examination (MMSE). Mortality data were obtained from the municipal registry.

The Integrated Systematic Care for Older Persons (ISCOPE) trial was conducted about 10 years after the Leiden 85-plus Study between 2009 and 2014 in Leiden, the Netherlands [54]. In ISCOPE, general practitioners (GPs) in and around Leiden recruited 1,921 patients aged ≥75 years. Nurses performed baseline and one-year follow-up measurements to assess baseline and outcome measurements on cognitive function, daily functioning and QoL in this cohort.

Using those data, **Chapters 3 and 4** describe the consequences of low SBP in old age under antihypertensive treatment. **Chapter 3** tests the association of low SBP and antihypertensive treatment with all-cause mortality and cognitive function from the general population of 85-year-olds in the Leiden 85-plus Study, who were followed up for five years. **Chapter 4** tests the association of low SBP and antihypertensive treatment with cognitive function, daily functioning, and QoL in the ISCOPE study, and includes patients ≥75 years with a one-year follow-up. Both studies further stratify their models for frailty and complex health problems.

Variation in antihypertensive treatment in old age, according to GPs

We sought to understand the role that frailty plays in GP decisions about treating hypertension in old age across countries and to see if those differences could be explained by country-specific cardiovascular disease burden and life expectancy.

The **A**ntihypertensive **T**rea**T**m**ENT I**n **V**ery **E**lderly (ATTENTIVE) Study is a collaborative research project. The ATTENTIVE Study enrolled GPs from 29 countries (26 European countries, and Brazil, Israel, and New Zealand) between March and July of 2016 [55, 56]. The only inclusion criteria for ATTENTIVE was that participants had to be practicing GPs. All participants were asked to answer an online survey that contained eight case vignettes of old patients (80 years) who consulted their GPs for a routine visit. The case vignettes differed in three characteristics: SBP of 140 or 160 mm Hg; CVD present or absent; and frailty (yes or no). For each case vignette, GPs were asked to decide if they would start antihypertensive treatment.

Chapters 5 and 6 focus on decisions GPs across 29 countries made about starting antihypertensive treatment when they were offered case vignettes of old patients. **Chapter 5** describes the international variation in GP decisions to start antihypertensive treatment in old age, and the ways patient characteristics affected this decision. **Chapter 6** describes our comparison of these countries, and accounts for country-specific CVD burden and life-expectancy at age 60.

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