PERSPECTIVES ON
TREATING HYPERTENSION
IN OLD AGE

The burden of polypharmacy, risks of treatment
and GPs' treatment probability

SVEN STREIT

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

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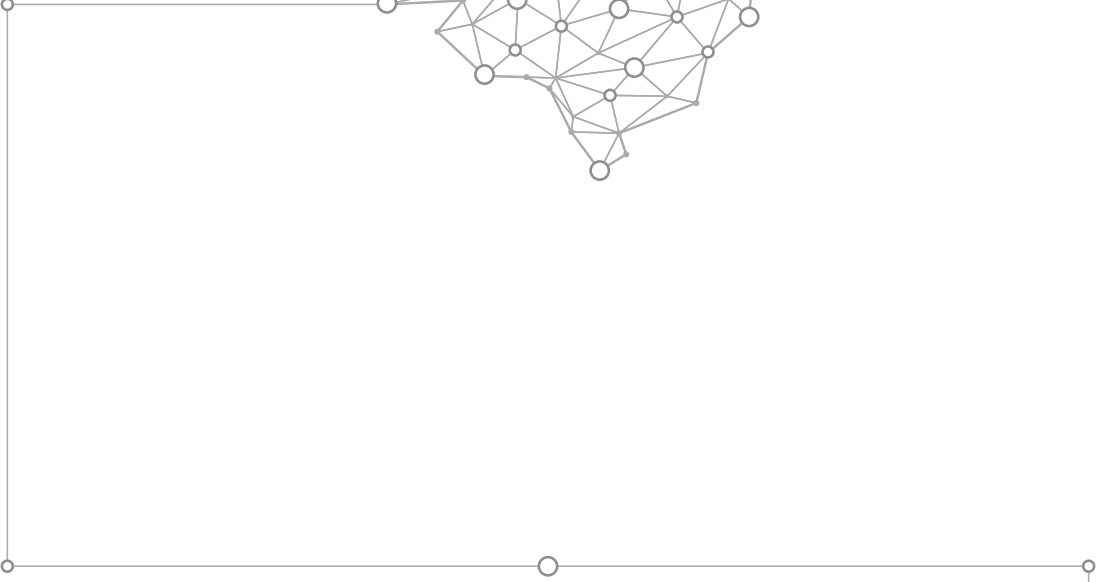Dr. E.P. Moll van Charante, Universiteit van Amsterdam
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CONTENTS

1

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.
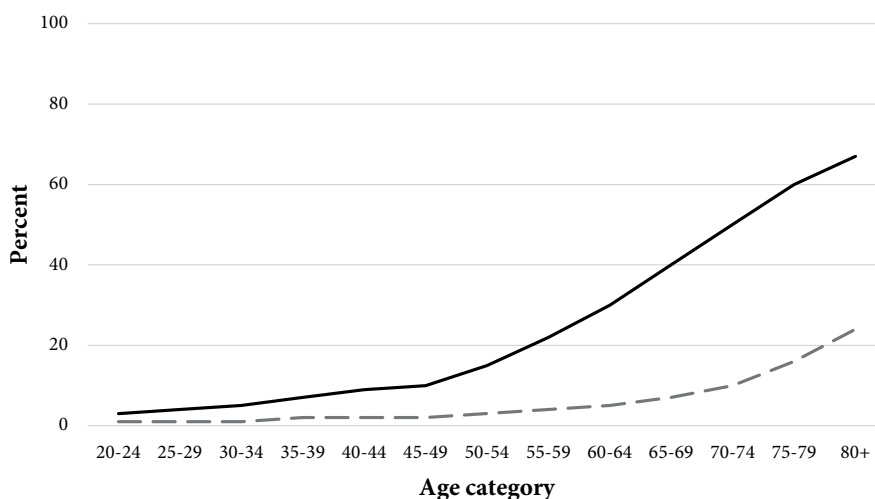

Figure 2. Increase of polypharmacy by age category. Solid line = 5 and more medications; dashed line = 10 or more medications. Adapted from [6].

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].
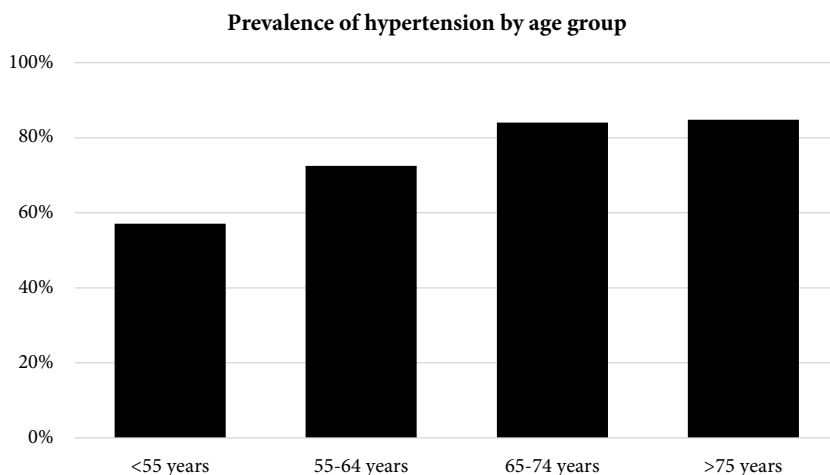
Prevalence of hypertension by age group

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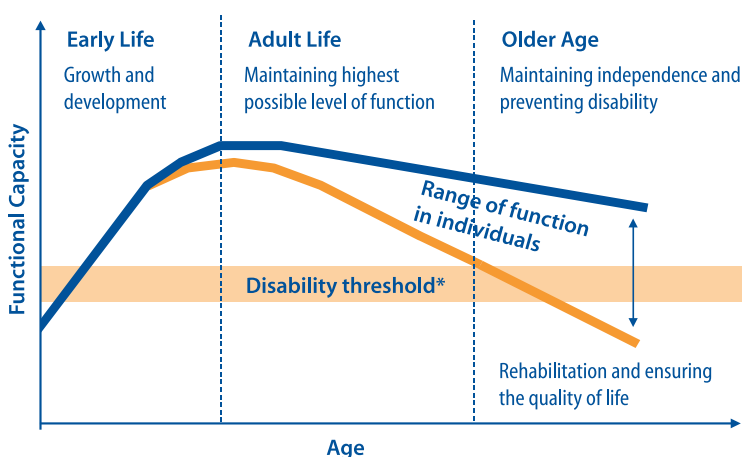

Figure 4. Heterogeneity in maintaining functional capacity over the life course [23].

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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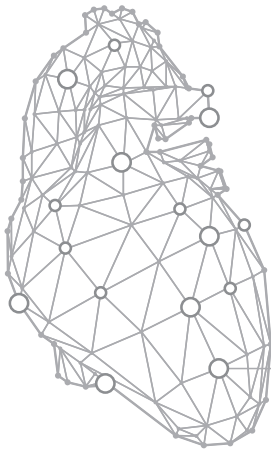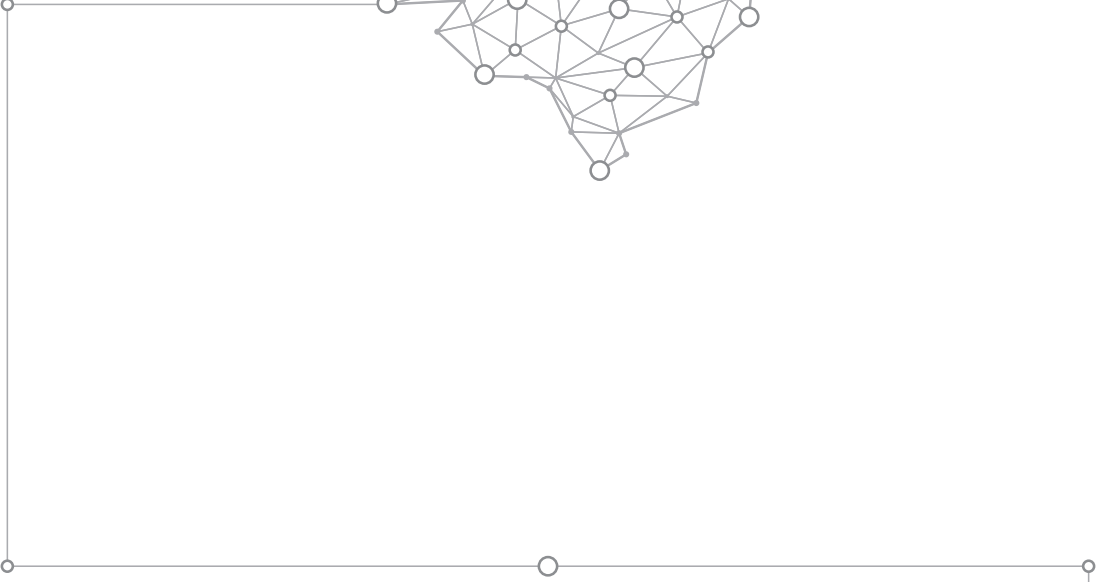
2

Polypharmacy and specific comorbidities in university primary care settings

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ABSTRACT

Background

Polypharmacy is associated with adverse events and multimorbidity, but data are limited on its association with specific comorbidities in primary care settings. We measured the prevalence of polypharmacy and inappropriate prescribing and assessed the association of polypharmacy with specific comorbidities.

Methods

We did a cross-sectional analysis of 1,002 patients aged 50-80 years followed in Swiss university primary care settings. We defined polypharmacy as ≥5 long-term prescribed drugs and multimorbidity as ≥2 comorbidities. We used logistic mixed-effects regression to assess the association of polypharmacy with the number of comorbidities, multimorbidity, specific sets of comorbidities, potentially inappropriate prescribing (PIP) and potential prescribing omission (PPO). We used multilevel mixed-effects Poisson regression to assess the association of the number of drugs with the same parameters.

Results

Patients (mean age 63.5 years, 67.5% ≥2 comorbidities, 37.0% ≥5 drugs) had a mean of 3.9 (range 0-17) drugs. Age, BMI, multimorbidity, hypertension, diabetes mellitus, chronic kidney disease, and cardiovascular diseases were independently associated with polypharmacy. The association was particularly strong for hypertension (OR 8.49, 95%CI 5.25-13.73), multimorbidity (OR 6.14, 95%CI 4.16-9.08), and oldest age (75-80 years: OR 4.73, 95%CI 2.46-9.10 vs.50-54 years). The prevalence of PPO was 32.2% and PIP was more frequent among participants with polypharmacy (9.3% vs. 3.2%, p<0.006).

Conclusions

Polypharmacy is common in university primary care settings, is strongly associated with hypertension, diabetes mellitus, chronic kidney disease and cardiovascular diseases, and increases potentially inappropriate prescribing. Multimorbid patients should be included in further trials for developing adapted guidelines and avoiding inappropriate prescribing.

INTRODUCTION

With the increasing life expectancy worldwide, a higher proportion of individuals not only get older [1], but are also more likely to develop multiple chronic conditions [2-4]. Most chronic conditions (comorbidities) are covered by disease-specific clinical guidelines using a single disease framework; this leads physicians to recommend drug treatments for each condition separately, which may lead to polypharmacy and drug-drug and drug-disease interactions [5]. In addition, to lower the risk of developing future medical conditions, research in preventive medicine has uncovered multiple risk factors, particularly in cardiovascular medicine, that also need treatment, thus increasing the number of people on regular multiple drug therapy [6, 7]. Furthermore, patients are often seen by multiple specialist physicians who prescribe drugs that primary care physicians are often reluctant to stop [8]. Polypharmacy, commonly defined as the concurrent use of 5 or more long-term prescribed drugs, is frequent and increasing in prevalence [4, 7, 9-14]. The use of multiple drugs is associated with potential unforeseen medical consequences, such as adverse drug events, drug monitoring errors, unplanned hospitalizations, and sometimes fatal outcomes [5, 15-19]. The risk of drug-drug interaction increases with the number of prescribed drugs: 13% of patients on 2 concurrent drugs experience drug-drug interaction, but this risk rises to 38% for those on 5 drugs and 82% for those on ≥7 drugs [20]. Moreover, polypharmacy is associated with poor adherence, lower physical and social function, higher healthcare costs, and decreased quality of life [13, 16, 19]. Additionally, inappropriate prescribing, including both over- (potentially inappropriate prescribing [PIP]) and underprescription (potential prescribing omission [PPO]) is also associated with poor outcome, such as increase in adverse drug events [21]. While polypharmacy is relatively well defined, the definition of multimorbidity is not consistent in the literature; a common definition is 2 or more comorbidities [3].

Prior epidemiological studies conducted in several other countries found a prevalence of polypharmacy ranging from 12 to 48% in patients aged 50 years or older [9, 10, 13, 14, 22], but data remain limited on associations between polypharmacy and specific comorbidities, like cardiovascular ones [13]. In Switzerland, a country with universal healthcare coverage, only one study assessed the prevalence of polypharmacy and PIP, based on claims data from a health insurer company without clinical information on diagnosis. Except for this study, data on PIP and PPO in Switzerland are limited, with studies including only hospitalized geriatric [23] or mentally-ill patients [24].

We therefore aimed to measure the prevalence of polypharmacy, PIP and PPO in university primary care settings, and to assess the association of polypharmacy with specific comorbidities, in order to uncover subgroups of patients at higher risk of polypharmacy.

MATERIAL AND METHODS

Study population

We abstracted medical records from 1002 randomly selected patients followed for at least one year by primary care physicians in all but one Swiss university primary care clinics (Basel, Geneva, Lausanne and Zurich) in a retrospective cohort study, as previously described [25]. For this analysis, we used cross-sectional data of the baseline visit. These community-dwelling patients were randomly identified from electronic administrative data of all patients aged 50 to 80 years and followed in 2005-2006. The selection was limited to this age group to ensure a high prevalence of cardiovascular risk factors and other conditions that are targeted by preventive care and medical treatment. About 90% of the patients were cared for by residents in general internal medicine supervised by senior physicians. The remaining 10% were cared by senior physicians directly.

We initially identified 1889 patients, among which 54 charts could not be found, probably because the patients had left the clinic for another ambulatory practice. We excluded 125 patients because they had no outpatient visit to a primary care physician, and 117 that were followed only in a specialized care setting during this period. In order to ensure adequate time and information to assess preventive care, we excluded another 591 patients who had less than one-year follow-up in the university primary care setting during the review period.

Definitions of polypharmacy and multimorbidity

We recorded only long-term prescribed drugs at the first visit of the review period; prescriptions for acute conditions, like antibiotics or temporary painkillers, were not taken into account. Similarly, to previous studies, we defined polypharmacy as 5 or more long-term prescribed drugs [9, 12, 14, 26, 27].

We found no consistent definition to select comorbidities in prior scientific literature [28]. The length of comorbidity lists ranged from 7 to 46 different comorbidities [13, 29-31]. We therefore established a new list including 17 comorbidities (Appendix table 1), as previously described [32], based on a large study by Higashi *et al.* [33] and on the Charlson index [34]. We added psychiatric conditions (e.g. schizophrenia, depression) as an important comorbidity [35], based on a consensus of the above mentioned references and between the authors. Additionally, we defined specific subgroups of comorbidities: 1) cardiovascular diseases: history of transient ischemic attack, cerebral vascular accident, coronary artery disease, angina, myocardial infarction, congestive heart failure and/or peripheral vascular disease; 2) chronic pulmonary diseases: chronic obstructive pulmonary disease, asthma, sleep apnea syndrome, sarcoidosis, pulmonary hypertension, bronchiectases, interstitial pulmonary disease and/or global respiratory insufficiency; 3) psychiatric diseases: depression, bipolar disorder, psycho-

sis, schizophrenia and/or pervasive development disorder. For sensitivity analyses, we used subcategories of cardiovascular disease (cerebral vascular disease, ischemic heart disease, heart failure). As did others [3, 29], we defined multimorbidity as the presence of 2 or more of these comorbidities [32], but also assessed the number of comorbidities as a count variable.

Potentially inappropriate prescribing and potentially prescribing omission

PIP and PPO were measured using the Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert doctors to Right Treatment (START) criteria [36]. As the criteria were developed for individuals aged ≥65 years, we applied them to this subgroup of our patients, and then performed a sensitivity analysis including our whole population. As we had detailed clinical information on cardiovascular disease and cardiovascular risk factors, we only applied the STOPP/START criteria for cardiovascular and anti-diabetic drugs when all detailed clinical information was available. Therefore, we applied 7 STOPP (i.e. A3, B3, B6, C1, C7, J1, J2) and 4 START (i.e. A3, A4, A5, A7) criteria related to these drugs. One author (CEA) checked the whole database for PIP and PPO. A 5% random sample was checked for accuracy by a second author (SS). The agreement between the 2 reviewers was 98.0% and the 2.0% disagreement was solved by discussion. PIP and PPO were defined as the percentage of patients with at least 1 unfulfilled STOPP and START criteria, respectively.

Statistical Analyses

We counted the number of drugs as a whole (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ≥10), as well as stratified by 5-year age groups and by the number of comorbidities (0, 1, 2, 3-4, 5-6, ≥7). We compared baseline characteristics between patients with and those without polypharmacy using t-test and chi-square test where appropriate.

We used a logistic mixed-effects regression model, crude and adjusted for age, gender, civil status and occupation, to assess the association of polypharmacy with the number of comorbidities, presence of multimorbidity, smoking status, body mass index (BMI), specific comorbidities, subgroups of comorbidities (psychiatric diseases, dementia, cardiovascular diseases, diabetes mellitus, hypertension, chronic pulmonary diseases, cancer and chronic kidney disease), PIP and PPO. Results were presented as odds ratio (OR) with 95% confidence intervals (CI).

We used a multilevel mixed-effects Poisson regression model, crude and adjusted for the same parameters, to assess the association between the number of drugs as a count variable with the same variables as in the previous model. Results were presented as incidence rate ratios (IRR) with 95% CI.

We used the mixed-effects models to account for the clustering of patients within the different treating physicians and treatment centres. We performed all statistical analyses using STATA release 13.1 (StataCorp, College Station, TX). All p-values were 2-sided at a 0.05 level of significance.

RESULTS

Patients characteristics

Table 1 shows baseline characteristics of the study population by presence or absence of polypharmacy. Mean age (standard deviation [SD]) was 63.5 (8.3) years and 44.4% were women. Most patients (55.9%) were Swiss and 37.9% were retired. The majority (67.5%) of patients had multimorbidity and the mean number of comorbidities was 2.6, ranging from 0 to 10. Almost every patient (91.1%) had at least 1 drug, 37.0% had polypharmacy and 4.1% had at least 10 drugs. The maximum number of different drugs taken by a single patient was 17.

Table 1. Patient characteristics: overall and by presence or absence of polypharmacy.

Characteristics	Overall (n=1,002)[a]	0-4 drugs (n=631, 63.0%)[a]	≥5 drugs (n=371, 37.0%)[a]	p-value[b]
Age, mean (SD)	63.5 (8.3)	62.2 (8.1)	65.7 (8.0)	<0.001
Age groups, n (% per column)				
50-54	197 (19.7)	156 (24.7)	41 (11.0)	<0.001
55-59	193 (19.3)	125 (19.8)	68 (18.3)	<0.001
60-64	186 (18.6)	118 (18.7)	68 (18.3)	<0.001
65-69	183 (18.3)	106 (16.8)	77 (20.8)	0.03
70-74	128 (12.3)	74 (11.7)	54 (14.6)	0.08
75-80	115 (11.5)	52 (8.2)	63 (17.0)	0.31
Women, n (% per column)	445 (44.4)	297 (47.1)	148 (39.9)	0.03
Civil status, n (% per column)				
married	506 (51.0)	314 (50.3)	192 (52.0)	<0.001
single	151 (15.2)	101 (16.2)	50 (13.6)	<0.001
divorced / separated	233 (23.5)	150 (24.0)	83 (22.5)	<0.001
widow/-er	103 (10.4)	59 (9.5)	44 (11.9)	0.14
Occupation, n (% per column)				
Employed	285 (29.0)	225 (36.3)	60 (16.6)	<0.001
Social aid	109 (11.1)	60 (9.7)	49 (13.5)	0.29
Unemployed	101 (10.3)	51 (8.2)	50 (13.8)	0.92
At home or in education	115 (11.7)	79 (12.7)	36 (9.9)	<0.001
Retired	372 (37.9)	205 (33.1)	167 (46.1)	0.049

Table 1. Patient characteristics: overall and by presence or absence of polypharmacy. (continued)

Characteristics	Overall (n=1,002)[a]	0-4 drugs (n=631, 63.0%)[a]	≥5 drugs (n=371, 37.0%)[a]	p-value[b]
Legal status, n (% per column)				
Swiss	560 (55.9)	362 (59.4)	198 (55.0)	<0.001
Resident permit	325 (32.4)	183 (30.2)	142 (39.4)	0.02
Forced migrant	81 (8.1)	61 (10.1)	20 (5.6)	0.002
Number of outpatients visits over 2 years				
Median (interquartile range)	10 (7-15)	9 (6-13)	12 (9-17)	<0.001
Range, minimum-maximum	2-63	2-41	3-63	
Never smoked, n (% per column)	283 (41.0)	194 (44.3)	89 (35.3)	0.02
BMI, mean (SD)	28.8 (5.6)	27.9 (5.3)	30.4 (5.8)	<0.001
Comorbidities[c]				
mean (SD)	2.6 (1.9)	1.9 (1.4)	3.7 (2.0)	<0.001
≥2 comorbidities, n (% per column)	676 (67.5)	346 (54.8)	330 (89.0)	<0.001
Specific subgroups[d], n (% per column)				
Psychiatric diseases[e]	294 (29.3)	180 (28.5)	114 (30.7)	0.46
Dementia	24 (2.4)	14 (2.2)	10 (2.7)	0.63
Cardiovascular diseases[f]	364 (36.3)	154 (24.4)	210 (56.6)	<0.001
Diabetes mellitus	292 (29.1)	113 (17.9)	179 (48.2)	<0.001
Hypertension	753 (75.1)	406 (64.3)	347 (93.5)	<0.001
Chronic pulmonary diseases[g]	261 (26.1)	148 (23.4)	113 (30.5)	0.02
Cancer	142 (14.2)	84 (13.3)	58 (15.6)	0.31
Chronic kidney disease	167 (16.7)	61 (9.7)	106 (28.6)	<0.001
Inappropriate prescribing				
Patients aged ≥65 years[a]				
PIP, n (% per column)	25 (5.6)	7 (3.0)	18 (9.3)	0.006
PPO, n (% per column)	137 (32.2)	80 (34.5)	57 (29.4)	0.26
Whole population				
PIP, n (% per column)	67 (6.7)	23 (3.7)	44 (11.9)	<0.001
PPO, n (% per column)	275 (27.5)	176 (28.0)	98 (26.4)	0.56

Abbreviations: PIP, potentially inappropriate prescribing; PPO, potentially prescribing omission; SD, standard deviation; STOPP, Screening Tool of Older People's Prescriptions; START, Screening Tool to Alert doctors to Right Treatment.

[a] For the subset of patients aged ≥65 years that were applied the STOPP/START criteria: total n was 426, with 194 (45.6% with polypharmacy and 232 (54.5%) without polypharmacy.

[b] p-value for comparison between patients with and without polypharmacy.

[c] list of 17 comorbidities listed in Appendix 1, full description in [32].

[d] record of ever having the listed comorbidity

[e] depression, bipolar disorder, psychosis, schizophrenia, pervasive development disorder.

[f] history of transient ischemic attack, cerebral vascular accident, coronary artery disease, angina, myocardial infarction, congestive heart failure or peripheral vascular disease.

[g] chronic obstructive pulmonary disease, asthma, sleep apnea syndrome, sarcoidosis, pulmonary hypertension, bronchiectases, interstitial pulmonary disease or global respiratory insufficiency.

The association between polypharmacy, number of drugs and age

Figure 1 (top) shows the percentage of patients on a particular number of drugs according to age group. Patients with polypharmacy were significantly older than patients on less than 5 drugs (p<0.0001, Table 1). The prevalence of polypharmacy was 20.8% (41/197) in the youngest age group (50-54 years), 45.6% (194/426) in the patients aged 65 years or older, and 54.8% (63/115) in the oldest age group (75-80 years). The oldest age group had the highest odds for polypharmacy compared to the youngest age group in adjusted analysis (OR 4.73, 95% CI 2.46-9.10, Table 2). In the highest age group, the number of drugs was 29% higher than in the lowest age group (IRR 1.29, 95% CI 1.07-1.56, Table 3).
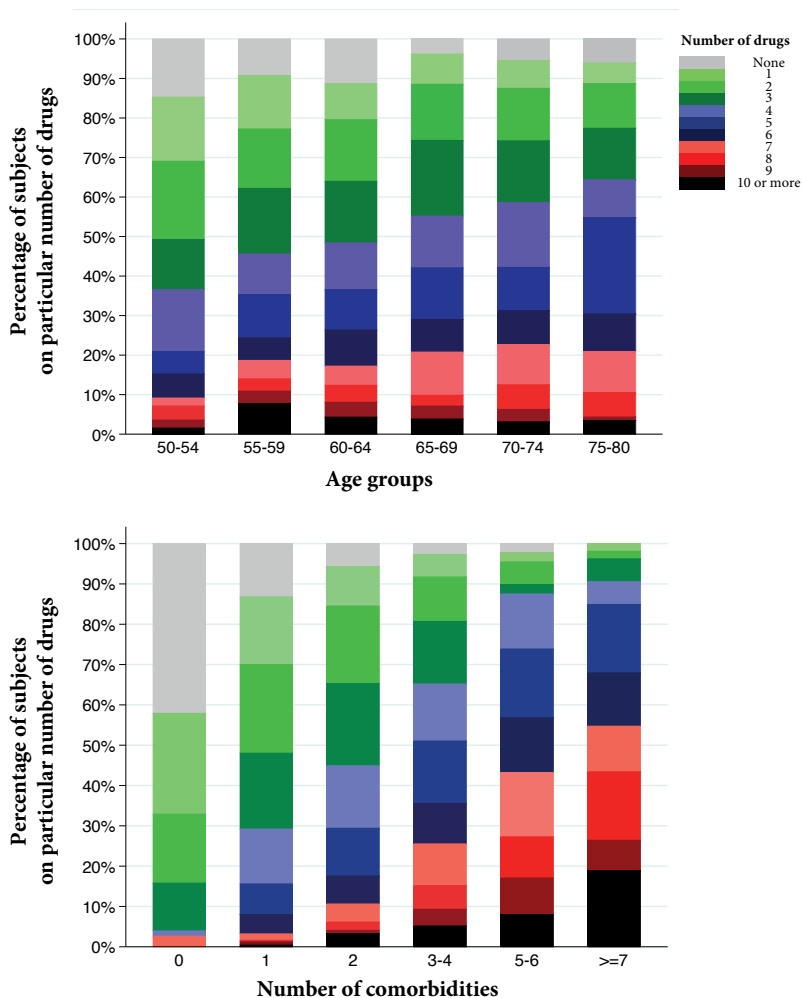
Figure 1. Percentage of patients in ambulatory medicine receiving a particular number of drugs (0 to ≥10), stratified by a) age groups; b) number of comorbidities (0, 1, 2, 3-4, 5-6, ≥7), out of a list of 17 selected comorbidities, based on a large study by Higashi et al. [33] and the Charlson index [34], as previously defined [32].

Table 2. Multivariate mixed-effects logistic regression analysis for the association between patient characteristics and polypharmacy.

Variable	Polypharmacy (≥5 drugs)	
	OR	95% CI
Age (years)[a]		
50-54 (reference)	1	-
55-59	2.14	1.31-3.51
60-64	2.16	1.30-3.59
65-69	2.71	1.52-4.84
70-74	2.78	1.46-5.27
75-80	4.73	2.46-9.10
Men	1.28	0.93-1.75
Civil status		
married (reference)	1	-
single	0.79	0.52-1.21
divorced / separated	0.95	0.67-1.36
widow/-er	1.01	0.63-1.61
Occupation		
Employed (reference)	1	-
Social aid	2.91	1.76-4.81
Unemployed	3.89	2.29-6.61
At home/in education	1.37	0.77-2.44
Retired	1.74	1.07-2.82
Never smoked	0.76	0.52-1.11
BMI (kg/m2), per unit	1.12	1.08-1.16
Comorbidities[b]		
Per each comorbidity	1.86	1.68-2.07
≥2 comorbidities versus 0-1 comorbidity	6.14	4.16-9.08
Specific subgroups[c]		
Psychiatric diseases[d]	1.14	0.83-1.59
Dementia	0.83	0.35-2.01
Cardiovascular diseases[e]	3.74	2.76-5.08
Diabetes mellitus	4.47	3.23-6.20
Hypertension	8.49	5.25-13.73
Chronic pulmonary diseases[f]	1.29	0.94-1.76
Cancer	0.97	0.65-1.45
Chronic kidney disease	3.96	2.71-5.80
Inappropriate prescribing		
Patients aged ≥65 years		
Potentially inappropriate prescription	3.72	1.47-9.44
Potentially prescribing omission	0.75	0.49-1.15

Table 2. Multivariate mixed-effects logistic regression analysis for the association between patient characteristics and polypharmacy. (continued)

Variable	Polypharmacy (≥5 drugs)	
	OR	95% CI
Whole population		
Potentially inappropriate prescription	3.64	2.07-6.39
Potentially prescribing omission	0.81	0.59-1.11

The model was adjusted for age, gender, civil status, occupation. Random-effects model was used to account for treating physician.

Some statistically significant variables in Table 1 lost significance because of the mixed-effects analysis.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] for univariate and multivariate analysis p-value for trend <0.001.

[b] list of 17 comorbidities listed in Appendix 1, full description in [32].

[c] record of ever having the listed comorbidity.

[d] depression, bipolar disorder, psychosis, schizophrenia, pervasive development disorder.

[e] history of transient ischemic attack, cerebral vascular accident, coronary artery disease, angina, myocardial infarction, congestive heart failure or peripheral vascular disease.

[f] chronic obstructive pulmonary disease, asthma, sleep apnea syndrome, sarcoidosis, pulmonary hypertension, bronchiectases, interstitial pulmonary disease or global respiratory insufficiency.

The association of polypharmacy, number of drugs and comorbidities

The number of drugs increased significantly with the number of comorbidities. In patients with 4 or more comorbidities, all but 2 patients (9.2%) had at least 1 drug. Among the patients with at least 7 comorbidities, 84.9% had polypharmacy (Figure 1 bottom). This association remained significant in multivariate analyses; even after adjustment for demographics, patients with multimorbidity had a far higher odds for polypharmacy (OR 6.14, 95% CI 4.16-9.08, Table 2) and an increased number of drugs (IRR 1.91, 95% CI 1.72-2.13, Table 3) compared to patients without multimorbidity. For each additional comorbidity, patients were more likely to have more prescribed drugs (IRR 1.18, 95% CI 1.15-1.20).

Hypertension had the strongest association with polypharmacy (OR 8.49, 95% CI 5.25-13.73) and the number of drugs (IRR 2.10, 95% CI 1.87-2.36). Cardiovascular diseases, diabetes mellitus, BMI and chronic kidney disease were also independently associated with polypharmacy and the number of drugs (Tables 2 and 3). Chronic pulmonary diseases were weakly associated with the number of drugs, but not with polypharmacy (Tables 2 and 3). Psychiatric diseases, dementia and cancer were associated neither with polypharmacy nor with the number of drugs. The OR (95%CI) for polypharmacy was 2.63 (1.56-4.46) in patients with cerebral vascular disease, 3.96 (2.75-5.71) in patients with ischemic heart disease, and 14.32 (5.75-35.66) in patients with heart failure.

Table 3. Multivariate categorical mixed-effects regression analysis for the association with number of drugs as a count variable.

Variable	Number of drugs (count variable)	
	Incident rate ratio	95% CI
Age (years)		
50-54 (reference)	1	-
55-59	1.27	1.11-1.45
60-64	1.24	1.07-1.44
65-69	1.30	1.10-1.53
70-74	1.29	1.09-1.53
75-80	1.29	1.07-1.56
Male	1.11	1.01-1.22
Civil status		
married (reference)	1	-
single	0.94	0.81-1.08
divorced / separated	0.97	0.86-1.08
widow/-er	1.05	0.92-1.19
Occupation		
Employed (reference)	1	-
Social aid	1.55	1.30-1.86
Unemployed	1.60	1.37-1.87
At home/in education	1.27	1.07-1.51
Retired	1.37	1.18-1.58
Never smoked	0.91	0.81-1.03
BMI (kg/m2), per unit	1.03	1.02-1.04
Comorbidities[a]		
Each comorbidity	1.18	1.15-1.20
≥2 comorbidities versus 0-1 comorbidity	1.91	1.72-2.13
Specific subgroups[b]		
Psychiatric disease[c]	1.11	1.00-1.23
Dementia	1.11	0.85-1.46
Cardiovascular disease[d]	1.48	1.35-1.63
Diabetes mellitus	1.58	1.45-1.72
Hypertension	2.10	1.87-2.36
Chronic pulmonary disease[e]	1.15	1.04-1.26
Cancer	1.01	0.89-1.14
Chronic kidney disease	1.52	1.37-1.69
Inappropriate prescribing		
Patients aged ≥65 years		
Potentially inappropriate prescription	1.35	1.12-1.64
Potentially prescribing omission	0.94	0.83-1.06

Table 3. Multivariate categorical mixed-effects regression analysis for the association with number of drugs as a count variable. (continued)

Variable	Number of drugs (count variable)	
	Incident rate ratio	95% CI
Whole population		
Potentially inappropriate prescription	1.44	1.26-1.64
Potentially prescribing omission	0.90	0.81-1.00

The model was adjusted for age, gender, civil status, occupation. Random-effects model was used to account for treating physician.

Some statistically significant variables in Table 1 lost significance because of the mixed-effects analysis.

Abbreviations: BMI, body mass index; CI, confidence interval.

[a] list of 17 comorbidities listed in Appendix 1, full description in [32].

[b] record of ever having the listed comorbidity.

[c] depression, bipolar disorder, psychosis, schizophrenia, pervasive development disorder.

[d] history of transient ischemic attack, cerebral vascular accident, coronary artery disease, angina, myocardial infarction, congestive heart failure or peripheral vascular disease.

[e] chronic obstructive pulmonary disease, asthma, sleep apnea syndrome, sarcoidosis, pulmonary hypertension, bronchiectases, interstitial pulmonary disease or global respiratory insufficiency.

Polypharmacy, number of drugs and other clinical variables

Being employed was associated with a lower number of drugs when compared with other social status (on social aid, unemployed, at home, in education, or retired), and with a lower prevalence of polypharmacy when compared with being on social aid or unemployed (Tables 2 and 3). These associations were less strong after adjusting for the number of comorbidities (data not shown). Civil status was associated neither with polypharmacy nor with the number of drugs. Finally, male gender was only slightly associated with the number of drugs, but not with polypharmacy (Tables 2 and 3).

Potentially inappropriate prescribing and potentially prescribing omission

Table 4 describes the prevalence of each STOPP/START criterion in patients aged ≥65 years and in the whole patient population. In patients aged ≥65 years, the prevalence of PIP was 5.9%; it was higher among patients with polypharmacy (9.3% versus 3.0% in those without, p=0.006, Table 1) and strongly associated with polypharmacy (OR 3.72, 95% CI 1.47-9.44, Table 2) and with the number of drugs (IRR 1.35, 95% CI 1.12-1.64, Table 3). Almost one third (32.2%) of the patients had PPO. PPO was associated neither with polypharmacy nor with the number of drugs (Tables 2 and 3). Forty-eight patients had more than 1 PPO. Omitting anti-platelet (START criterion A3) and statin (START criterion A5) therapies with a documented history of coronary, cerebral, or peripheral vascular disease were the 2 most prevalent PPO, accounting for 70.7% of the PPOs. We found similar results in the whole study population (Tables 2, 3 and 4).

Table 4. Number of patients with unfulfilled STOPP/START criteria.

	Patients ≥65 years, (n=426)	All patients (n=1,002)
STOPP criteria		
A3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	5 (1.2)	7 (0.7)
B3. Beta-blocker in combination with verapamil or diltiazem	1 (0.2)	4 (0.4)
B6. Loop diuretic as first-line treatment for hypertension	1 (0.2)	4 (0.4)
C1. Long-term aspirin at doses greater than 160mg per day	8 (1.9)	17 (1.7)
C7. Ticlopidine in any circumstances	0 (0.0)	0 (0.0)
J1. Sulphonylureas with a long duration of action with type 2 diabetes mellitus	12 (2.8)	37 (3.7)
J2. Thiazolidinediones in patients with documented heart failure	0 (0.0)	0 (0.0)
START criteria		
A3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease	63 (14.8)	129 (12.9)
A4. Antihypertensive therapy where systolic blood pressure consistently >160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure >140 mmHg and /or diastolic blood pressure >90 mmHg, if diabetic	15 (3.5)	53 (5.3)
A5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 years.	77 (18.1)	153 (15.3)
A7. Beta-blocker with ischaemic heart disease.	43 (10.1)	72 (7.2)

Abbreviations: STOPP, Screening Tool of Older People's Prescriptions; START, Screening Tool to Alert doctors to Right Treatment. Data are presented as number (%) of patients.

DISCUSSION

In this random sample of primary care patients aged 50-80 years, we found that 37% had polypharmacy, and 4% received 10 drugs or more. The prevalence of PIP was significantly higher among patients with polypharmacy. Multimorbidity, age, and specific comorbidities, such as hypertension, diabetes mellitus, chronic kidney disease and cardiovascular diseases, were associated with polypharmacy, while other subgroups of comorbidities (psychiatric diseases, dementia, chronic pulmonary diseases, cancer) were not. The association was particularly strong for hypertension.

The prevalence of polypharmacy in our study was consistent with prior epidemiological studies conducted in other high income countries in patients aged 50 years or older: a large Swedish study found a prevalence of polypharmacy of 12-38% in the age group 50-79 years [9], while it ranged from 13 to 48% for the same age range in a study using electronic primary care records in Scotland [13], and was 29% in patients aged 57-85 years in the USA [14]. When focusing on

patients aged 65 years or older, the prevalence of polypharmacy in our study (46%) was also consistent with previous data from an Italian community-dwelling population (46%) [22].

The strong association of multimorbidity and the number of comorbidities with polypharmacy and the number of drugs is consistent with previous data [13, 14, 31]. This may reflect the disease-specific guidelines that are still usually applied for initiating drug treatments. However, patients with multimorbidity are often excluded from, and less than 5% explicitly included in randomized controlled trials on which these recommendations are based [37]; thus, applying them to these patients may be inappropriate [19, 38]. The strong association between PIP and polypharmacy is consistent with previous data using the same criteria for PIP [23]. This observation highlights the importance to reconsider each prescription in patients receiving polypharmacy. For this purpose, the STOPP/START criteria may help [36, 39]; however, as the application of the whole criteria set is time-consuming and therefore difficult to implement in everyday clinical practice, software solutions are under development. Finally, physician's clinical judgment and shared decision making are central in the process of prescription.

The United Kingdom Prospective Diabetes Study (UKPDS) in patients with type 2 diabetes showed that 29% of the patients needed at least 3 different drugs to reach a blood pressure target of <150/85mmHg [40], while the recommended goal in this population is far lower (<130/80mmHg) [41]. Additionally, because hypertension, diabetes mellitus and chronic kidney disease are strongly related to cardiovascular diseases, patients with these comorbidities often receive additional drugs recommended in both primary and secondary prevention (e.g. aspirin, statins) [19, 42-44]. The association of these cardiovascular risk factors and cardiovascular diseases with polypharmacy is consistent with previous data [13, 45]. Interestingly, we found a stronger association of polypharmacy with hypertension than with cardiovascular disease. The interpretation of this finding is limited by our broad classification of cardiovascular disease, which was associated with some heterogeneity (e.g. stronger association of polypharmacy with heart failure than with stroke).

Surprisingly, we found no association between polypharmacy and psychiatric disorders. This probably reflects the reality of patients cared in ambulatory general internal medicine. Psychiatric conditions that are mostly managed with drugs (e.g. schizophrenia) [46] were indeed rather rare (6% of the patients having a psychiatric condition in our study had schizophrenia), while more prevalent conditions like personality disorder (25% of the patients having a psychiatric condition in our study) are often managed without any drug as first line therapy. On the other hand, patients followed in specialized psychiatric settings may have more severe conditions needing multiple medications, thus polypharmacy may be more prevalent among them. We also found no association with dementia, but our study included only 24 patients

with this condition. Preventive drugs might have been discontinued in these patients with formally diagnosed dementia, as dementia is associated with shortened life expectancy and decreased quality of life [47].

In our study, there was no significant association between cancer and polypharmacy, which is consistent with the study by Payne et al. (12) that found a similar mean number of drugs among this subgroup of patients (4 drugs). On the opposite, a review of previous studies in patients with advanced cancer showed a high prevalence of polypharmacy among them [48]. This discrepancy is probably due to different settings (in-hospital versus ambulatory) and study population (advanced versus not advanced cancer).

Patients who were unemployed, receiving social aid, at home, in education or retired, were prescribed a higher number of drugs than patients that were employed. Interestingly, this association was stronger for patients unemployed or receiving social aid than for patients being at home, in education or retired. This finding may be partially explained by a higher number of comorbidities, as the association of occupation status and polypharmacy was weakened by adjusting for the number of comorbidities. This is consistent with data showing a higher prevalence of multimorbidity in the most deprived population, among which multimorbidity would occur on average 10 to 15 years earlier [3]. However, as this association didn't disappear after adjustment for the number of comorbidities, we can hypothesize additional explanations for this finding: deprived patients may have lower income and/or education, which has been associated with polypharmacy [10, 13, 49]; they may also more likely consult with a prescription purpose, as suggested previously [49].

Although the community-dwelling individuals in our study differed from older frail nursing home residents, those with multimorbidity are at higher risk of polypharmacy as they become older. Although the patterns of drugs are different in nursing home and in the community, e.g. with a higher number of pain-killers and psychotropic drugs [50-52], optimizing medication in the community-dwelling individuals is also central in order to optimize care and reduce polypharmacy.

There are some limitations to our study. First, our results are based on retrospective medical chart review, with potential underreporting; however, a previous study comparing process-based quality scores using standardized patients, clinical vignettes and abstraction of medical charts found that measurement of quality of care using abstraction of medical charts was about 5% lower than using clinical vignettes and 10% lower than using standardized patients [53]. Second, we restricted our analyses to patients aged 50 to 80 years and can therefore not draw conclusions for younger or older patients. Third, as we could apply a subset of the STOPP/START criteria only, we could not compare the prevalence of PIP and PPO with data

of other previous studies. Fourth, we conducted only a cross-sectional analysis without assessing the impact of polypharmacy and STOPP/START criteria on patient's related health outcomes Finally, our results may not be totally generalizable to primary care settings in general for several reasons: we could not assess other parameters of socioeconomic status, such as income and education, because of the lack of reliable information on these variables in the medical charts, and, in Switzerland, there are generally more forced migrants and patients with lower socioeconomic status in university primary care settings, which has been associated with an earlier occurrence of multimorbidity [3]. The prevalence of some comorbidities, like hypertension, may also be higher in these settings [32]. Furthermore, almost all patients were cared by residents at the end of their postgraduate training, who may be more adherent to medical guidelines [25].

Conclusions

In this random sample of primary care patients, we found that polypharmacy was highly prevalent in university primary care settings and strongly associated with age, multimorbidity, the number of comorbidities, and specific comorbidities, particularly hypertension, diabetes mellitus, chronic kidney disease, and cardiovascular diseases. This is clinically relevant, given the association of polypharmacy with adverse consequences, particularly in patients with multimorbidity [5]. Given that the prevalence of polypharmacy and multimorbidity will very probably further increase in the coming years, and that PIP is associated with polypharmacy, further randomized trials including multimorbid patients are needed in order to develop guidelines adapted to this particular population to help avoiding PIP and adverse drug events. As polypharmacy, the risk for drug-drug interactions and their associated negative consequences are significantly increased among the oldest old patients because of frailty and their higher number of comorbidities [54], future studies should also plan to include oldest old patients, i.e. those aged more than 80 years. Waiting for any new specific recommendation for multimorbid elderly, specific indications for each drug should be very carefully reviewed, particularly in those patients. In the meantime, we suggest that the process of prescription relies on the use of criteria developed to avoid PIP and PPO (e.g. the STOPP/START criteria [36, 39]), accounting for physician's clinical judgment, estimated patient's life expectancy and patient's preferences.

Appendix Table 1. List of 17 selected comorbidities[a] in ambulatory medicine

Condition	Prevalence, n (%)
Hypertension	743 (75.2)
Diabetes mellitus	292 (29.1)
COPD, Asthma	261 (26.1)
Depression	197 (19.7)
Coronary artery disease[b]	190 (19.0)
Renal insufficience[c]	167 (16.7)
Cancer[d]	142 (14.2)
Other psychiatric diseases[e]	97 (9.7)
Stroke (or carotid endarterectomy, hemiplegia)	86 (8.6)
Liver disease (cirrhosis, hepatitis B/C)	63 (6.3)
Gastrointestinal disease[f]	52 (5.2)
Connective tissue disease	51 (5.1)
Heart failure	47 (4.7)
Peripheral vascular disease (angioplasty, foot amputation)	37 (3.7)
Major neurologic disease[g]	29 (2.9)
Dementia	24 (2.4)
AIDS	13 (1.3)

[a] Based on previous studies [32] and the Charlson index [34].

[b] Coronary artery disease, angina, myocardial infarction, other coronary heart disease, coronary angioplasty, coronary bypass

[c] End-stage renal disease, dialysis, kidney transplant, diabetic nephropathy or hypertensive nephropathy

[d] Solid non-metastatic, solid metastatic cancer, leukemia, lymphoma

[e] Bipolar disorder, psychosis, schizophrenia, pervasive developmental disorder, spastic paresis

[f] Gastric ulcus or pancreatitis or Crohn's disease or ulcerative colitis

[g] Multiple sclerosis, epilepsy, medullary compression, Parkinson, Polio or spastic paresis

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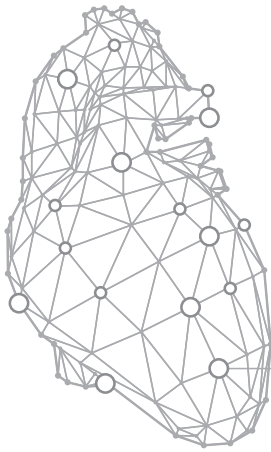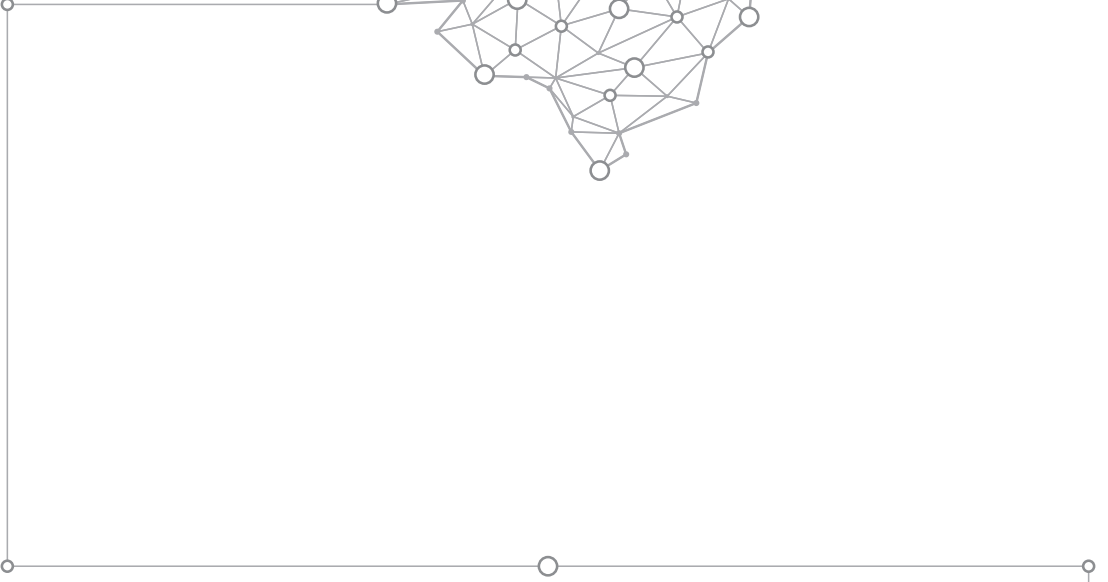
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Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old – data from the Leiden 85-plus Study

Sven Streit, Rosalinde KE Poortvliet, Jacobijn Gussekloo

ABSTRACT

Background

The appropriateness of lowering systolic blood pressure remains controversial in the oldest-old. We tested whether systolic blood pressure is associated with all-cause mortality and change in cognitive function for patients prescribed antihypertensive treatment and those without treatment.

Methods

We studied participants in the population-based Leiden 85-plus cohort study. Baseline systolic blood pressure and use of antihypertensive treatment were predictors; all-cause mortality and change in cognitive function measured using the Mini-Mental State Examination were the outcomes. Grip strength was measured as a proxy for physical frailty. We used Cox proportional hazards and mixed-effects linear regression models to analyse the relationship between systolic blood pressure and both time to death and change in cognitive function. In sensitivity analyses we excluded deaths within one year and restricted analyses to participants without a history of cardiovascular disease.

Results

Of 570 participants, 249 (44%) were prescribed antihypertensive therapy. All-cause mortality was higher in participants with lower blood pressure prescribed antihypertensive treatment (HR 1.29 per 10mmHg lower systolic blood pressure, 95% CI 1.15-1.46, p<0.001). Participants taking antihypertensives showed an association between accelerated cognitive decline and lower blood pressure (annual mean change -0.35 points per 10mmHg lower systolic blood pressure, 95% CI -0.60, -0.11, p=0.004); decline in cognition was more rapid in those with lower handgrip strength. In participants not prescribed antihypertensive treatment, no significant associations were seen between blood pressure and either mortality or cognitive decline.

Conclusions

Lower systolic blood pressure in the oldest-old taking antihypertensives was associated with higher mortality and faster decline in cognitive function.

INTRODUCTION

Hypertension is the most important preventable cause of cardiovascular disease (CVD), including stroke and myocardial infarction [1]. The prevalence of hypertension increases sharply with age [2]. It has been clear for at least two decades that older patients (>60 years) also benefit from antihypertensive treatment [3, 4], but guidelines may not apply equally to everyone over 60 years. For example, we do not know if the effects of treating hypertension are similar among individuals aged over 80 years (the oldest-old) – a segment of the population that is expected to triple in the next two decades [5].

Hypertension studies have tended to exclude patients with multimorbidity and frailty. These criteria disproportionately exclude the oldest-old because this age group are much more likely to have multimorbidity or to be frail [6, 7]. At the same time, observational studies have raised concerns about associations between low systolic blood pressure (SBP), increased mortality and accelerated cognitive decline, especially in the oldest-old living with frailty [8]. Studying associations between SBP and cognitive decline is challenging [9]. There is evidence that high SBP in midlife damages cerebral vessels and impairs brain function [10], but low SBP in late life, particularly in frail subjects, is associated with higher risk for cognitive decline [11]. A study by Mosello *et al.* found that lower SBP was associated with faster cognitive decline in individuals who were already cognitively impaired [12]; several other studies had produced similar findings [13-19]. Mosello *et al.* were the first to describe that antihypertensive therapy modified these associations: low SBP was associated with cognitive decline only in patients under antihypertensive therapy, but not in those who were not prescribed antihypertensive therapy. Unfortunately, the follow-up time was too short to detect long-term protective effects of antihypertensive treatment, and the population was limited to patients attending a memory clinic.

There is therefore a need for rigorous, population-based observational studies with adequate follow up time to test the association between antihypertensive therapy, blood pressure, mortality and cognitive decline in the oldest-old. We analysed data from a population-based cohort study with a five-year follow-up to test if the association between low SBP with all-cause mortality and cognitive function differs for oldest-old patients under antihypertensive treatment and those without treatment, and to test if frailty modifies these associations.

METHODS

Study design and setting

We analysed data from a prospective, population-based cohort study with a five-year follow up - the Leiden 85-plus Study [20, 21]. All inhabitants of the city of Leiden, the Netherlands, were invited to join this cohort study if they turned 85 years between 1997-1999. No exclusion criteria were applied. The target population was 705 inhabitants. Of these, 14 (2.0%) died before being enrolled in the study; 599 (85.0%) provided informed or proxy consent [22]. The Medical Ethical Committee of the Leiden University Medical Center approved the original study.

Participants

For this analysis, we applied two prespecified exclusion criteria. To lower the risk of reverse causality between SBP and mortality risk, we excluded participants who died less than 3 months after they entered the cohort (n=5). We also excluded participants who had no SBP measurements at baseline (n=24).

Procedures and measurements

A history of cardiovascular disease (i.e. previously recorded diagnoses of angina pectoris, myocardial infarction, heart failure, intermittent claudication, peripheral arterial surgery, transient ischaemic attack, and stroke) was available from General practitioners (GPs) or nursing home physicians. At baseline, research nurses visited all participants to administer the Mini-Mental State Examination (MMSE) [23]. At baseline, SBP was measured twice with a mean time range between measurements of 2 weeks. SBP was measured using a mercury sphygmomanometer, in the seated position after at least 5 min of rest and with no vigorous exercise in the preceding 30 min. For this analysis, we averaged the two measurements of SBP. The research nurses also recorded socio-demographic characteristics (level of education, income, living place); current smoking status (yes/no); depressive symptoms if MMSE was >18 points using the 15-point Geriatric Depression Scale [24]; and hand grip strength using a hand dynamometer. During annual follow-up visits, nurses repeated MMSE measurements. All participants were followed for all-cause mortality for 5 years using municipal records.

Statistical Analysis

We assessed associations between exposure (baseline SBP and use of antihypertensive medi-cation) and outcomes (all-cause mortality and annual change in cognitive function) over 5 years. At baseline, we compared characteristics of participants prescribed and not prescribed antihypertensive therapy. The crude and adjusted modelling approaches for all-cause mortal-ity using Cox proportional hazard models and annual change in MMSE using mixed-effects linear regression models are described in detail in Appendix text. Subgroup analyses were

performed for the second aim, to test if grip strength (as a proxy for frailty) modified the associations of SBP and treatment with the outcomes. We stratified both models for low/high hand grip strength to explore effect sizes and directions of effects. However, due to small sample sizes, this subgroup analysis was only exploratory. In sensitivity analyses, we firstly excluded deaths within 1 year after baseline; secondly restricted the models to participants without a history of CVD at baseline; and thirdly recoded participants who could not perform the hand grip strength test as missing. A two-sided P-value of 0.05 was taken as statistically significant for all analyses. We used STATA 15.0 (StataCorp, College Station, TX, USA) for all analyses.

RESULTS

We analysed data from 570 individuals, of whom 249 (43.7%) were prescribed antihypertensive therapy at baseline (Table 1). Participants prescribed antihypertensive therapy and those not prescribed antihypertensives were similar in all aspects except for a higher prevalence of CVD in those prescribed antihypertensives (61.9% vs. 35.8%, p<0.001). The other cardiovascular, socio-demographic, and functional characteristics at baseline were equally distributed among the two groups.

Appendix table 1 describes the sample of 214 participants grouped in lowest/highest SBP quintile. In the group prescribed antihypertensive therapy, participants with SBP <140 mmHg were more often institutionalized than those with SBP >170 mmHg (33.3% vs. 4.7%, p=0.001), and had slightly lower baseline MMSE (median 26 vs. median 27, p=0.021). The same pattern was evident in participants not prescribed antihypertensive therapy.

All-cause mortality over time

Figure 1 shows Kaplan-Meier survival curves for participants in the highest and lowest quintiles of SBP. Those prescribed antihypertensive therapy with SBP >170 mmHg had the lowest risk of all-cause mortality, and those with SBP <140mmHg had the highest risk (log rank test p<0.001).

During the 5-year follow-up, 263 (46.1%) participants died. For those participants prescribed antihypertensive therapy, all-cause mortality was significantly higher with decreasing SBP (HR 1.29 per 10mmHg lower SBP, 95%CI 1.15-1.46, p<0.001) (Table 2). For those not prescribed antihypertensives, the effect was smaller and did not reach significance (HR 1.08 per 10mmHg

Table 1. Baseline characteristics of participants at age 85 years by antihypertensive treatment (*n*=570).

Domains	Overall (*n*=570)	Antihypertensive treatment (*n*=249)	No antihypertensive treatment (*n*=321)	P-value[a]
Sociodemographic characteristics				
Women, n (%)	380 (66.7)	173 (69.5)	207 (64.5)	0.21
Low education[b], n (%)	358 (64.9)	163 (66.8)	195 (63.3)	0.39
Low income[c], n (%)	280 (50.9)	122 (50.8)	158 (51.0)	0.98
Institutionalized, (%)	102 (18.4)	45 (18.4)	57 (18.3)	0.97
Cardiovascular characteristics				
SBP in mmHg, mean (SD)[d]	155.2 (18.7)	154.8 (16.8)	155.5 (20.0)	0.64
Current Smoker, n (%)	89 (15.7)	33 (13.3)	56 (17.6)	0.16
Diabetes mellitus, n (%)	91 (16.3)	46 (18.9)	45 (14.2)	0.14
CVD[e], n (%)	269 (47.2)	154 (61.9)	115 (35.8)	<0.001
Functional characteristics				
Cognition (MMSE [f]), median (IQR)	26 (22-28)	26 (21-28)	26 (23-28)	0.094
Depression (GDS[g]), median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.70
Low hand grip strength[h], n (%)	362 (63.5)	161 (64.7)	201 (62.6)	0.62

[a] Chi-square test for categorical variables, t-test for normally distributed continuous and Wilcoxon rank-sum test for non-normally distributed data was used

[b] defined as primary school only

[c] defined as state pension only (about EUR 750 monthly)

[d] SBP = systolic blood pressure was measured twice during home visit at baseline in a seated position, two weeks apart, and after at least 5 minutes of rest and no vigorous exercise in the preceding 30 minutes. Both measurements were averaged.

[e] CVD included angina pectoris, myocardial infarction, heart failure, intermittent claudication, peripheral arterial surgery, TIA, and stroke

[f] MMSE, possible scores range from 0 to 30 points (worst to best). Missing data in n=7.

[g] GDS-15, possible scores range from 0-15 (worst to best). Data not available for participants with Mini-Mental State Examination (MMSE) scores <18 (n=97).

[h] Participants with hand grip strength below the sex-specific medians or unable to perform the test (n=35)

lower SBP, 95% 1.00-1.18, p=0.057). The sensitivity analyses returned similar results in the model excluding deaths (n=47) within 1-year after baseline (Appendix table 2) and when the model was restricted to participants with no history of CVD at baseline.

Change of cognitive function over time

Figure 2 describes the median annual change in MMSE for those in the highest and lowest quintiles of SBP, both for those prescribed antihypertensives and those not prescribed antihypertensives. In the group prescribed antihypertensives, those with SBP in the lowest quintile showed faster cognitive decline compared to those in the highest SBP-quintile (-1.1 points per year [IQR 1.4] vs -0.1 points per year [IQR 0.6]; p=0.022). For those not prescribed

antihypertensive therapy, no significant difference between the lowest and highest quintiles of blood pressure was evident (-0.7 points per year [IQR 2.2] vs. -0.5 points per year [IQR 1.4]; p=0.46).
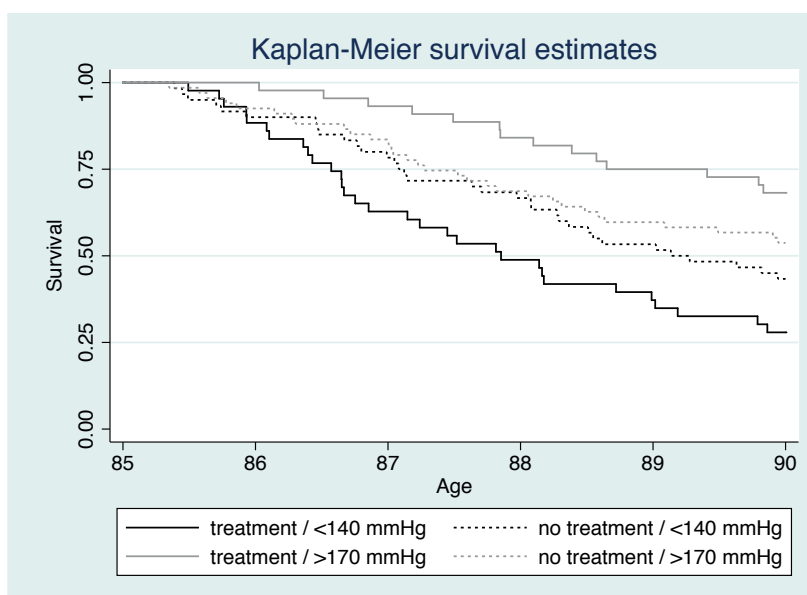
Figure 1. Kaplan-Meier survival curves for all-cause mortality grouped by under/without antihypertensive therapy and lowest/highest quintile of systolic blood pressure. All participants were aged 85 years when included in the study and followed-up to a maximum of 5 years.

Table 2. Subgroup analysis for hand grip strength and associations of systolic blood pressure (SBP) and all-cause mortality per 10 mmHg lower SBP (n=570)

		Hazard ratio (95% CI) per 10 mmHg lower SBP	P-value
Treatment			
Overall[a] *(n=249)*		*1.29 (1.15, 1.46)*	*<0.001*
By hand grip strength[b]	Low (n=161)	1.24 (1.08, 1.42)	0.002
	High (n=88)	1.40 (1.09, 1.80)	0.009
No treatment			
Overall[a] *(n=321)*		*1.08 (1.00, 1.18)*	*0.057*
By hand grip strength[b]	Low (n=201)	1.10 (1.00, 1.21)	0.060
	High (n=120)	0.99 (0.86, 1.15)	0.90

[a] Participants during and without antihypertensive treatment, adjusted for sex and cardiovascular disease
[b] Participants who were unable to perform the test (n=35) were classified to be low in hand grip strength, adjusted for sex and cardiovascular disease

Annual change in cognitive function from age 85 up to 90 by antihypertensive treatment and systolic blood pressure at baseline

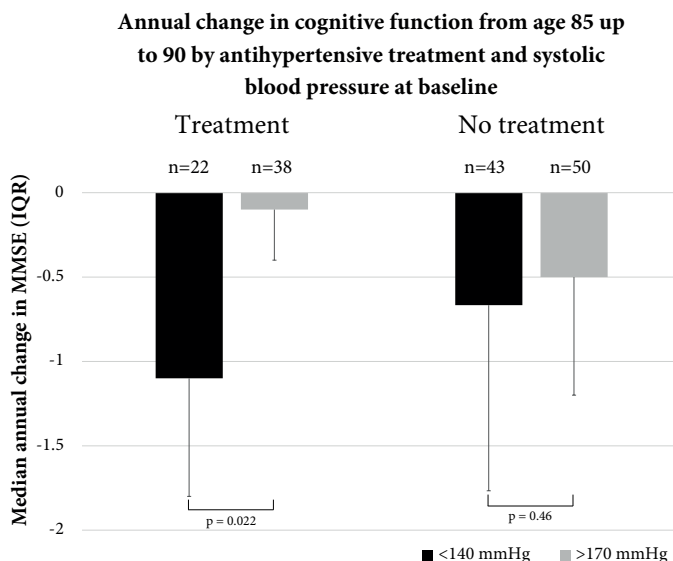**Figure 2.** Annual change in cognitive function (measured by the Mini-Mental State Examination, MMSE) grouped by under/without antihypertensive therapy and lowest/highest quintile of systolic blood pressure.

After accounting for baseline differences, those prescribed antihypertensives showed a faster rate of decline in MMSE with lower blood pressure (annual change in MMSE of -0.35, 95% CI -0.60 to -0.11 per 10mmHg drop in SBP; p=0.004). For those not prescribed antihypertensive therapy, the rate of decline was not significantly faster with lower baseline blood pressure (annual change in MMSE -0.14, 95% CI -0.39 to 0.11 per 10mmHg drop in SBP; p=0.28) (Table 3). The sensitivity analysis returned similar results when the model was restricted to participants with no history of CVD at baseline.

Modification by frailty

Our results did not change in our subgroup analyses for all-cause mortality (Table 2), when we stratified by low or high hand grip strength in participants prescribed antihypertensive therapy (p for interaction=0.28) or not prescribed antihypertensive therapy (p for interaction=0.29). There was weak evidence for an association in those participants not prescribed antihypertensives who had low hand grip strength (HR 1.10, 95% CI 1.00 to 1.21, p=0.060).

The subgroup analyses for annual change in cognitive function (Table 3) showed that accelerated change in MMSE with lower SBP was significant for those under antihypertensive therapy when they had low hand grip (annual change in MMSE -0.37, 95% CI -0.70 to -0.05 per 10mmHg drop in SBP; p=0.023) but did not reach significance for those with high hand grip strength (annual change in MMSE -0.24, 95% CI -0.57 to 0.09 per 10mmHg drop in SBP;

Table 3. Subgroup analysis for hand grip strength and changes in cognitive function measured by the Mini-Mental State Examination (MMSE) according to systolic blood pressure (SBP) at age 85 (per 10 mmHg lower SBP).

		Baseline difference		Annual change		Accelerated change	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Treatment							
Overall[a] (n=220)		-0.33 (-0.63, -0.03)	0.032	+1.20 (-0.50, +2.91)	0.17	-0.35 (-0.60, -0.11)	0.004
By hand grip strength[b]	Low (n=141)	-0.38 (-0.78, +0.02)	0.061	+1.14 (-1.18, +3.45)	0.34	-0.37 (-0.70, -0.05)	0.023
	High (n=79)	-0.04 (-0.47, +0.39)	0.84	+0.87 (-1.30, +3.05)	0.43	-0.24 (-0.57, +0.09)	0.15
No treatment							
Overall[a] (n=284)		-0.72 (-1.00, -0.44)	<0.001	-0.62 (-2.39, +1.16)	0.50	-0.14 (-0.39, +0.11)	0.28
By hand grip strength[b]	Low (n=172)	-0.80 (-1.20, -0.40)	<0.001	-0.90 (-3.60, +1.79)	0.51	-0.13 (-0.49, +0.24)	0.50
	High (n=112)	-0.18 (-0.49, +0.12)	0.23	-0.76 (-2.13, +0.61)	0.28	-0.04 (-0.24, +0.17)	0.74

'Baseline difference' means the association per 10 mmHg lower SBP and MMSE at baseline. 'Annual change' indicates the annual difference in MMSE over time until age 90. 'Accelerated change' is the additional change in MMSE over time associated per 10 mmHg lower SBP.

[a] Participants with and without antihypertensive treatment, adjusted for sex and cardiovascular disease

[b] Participants unable to perform the test (n=35) were classified to have less hand grip strength, adjusted for sex and cardiovascular disease

p=0.15). There was no evidence of interaction of hand grip strength in those without therapy (p for interaction=0.10). The sensitivity analysis returned similar results when participants who could not perform the hand grip strength test were classified as missing data instead of categorized as having low hand grip strength.

DISCUSSION

In this population-based cohort of individuals aged 85 years with a 5-year follow-up, we found lower SBP was associated with higher all-cause mortality and faster annual cognitive decline in participants prescribed antihypertensive therapy. In participants without antihypertensive treatment, no relation was found between SBP and mortality or cognitive decline. Low grip strength did not modify the association of SBP and mortality but did for cognitive decline.

Our findings are in line with other cohort studies showing the same associations of low SBP and increased mortality although previous analyses did not stratify for antihypertensive treatment [25, 26]. For cognition, age seems to modify the associations; in studies with patients aged >60 there was either no association between SBP and cognitive decline [27] or an association of higher SBP with a lower risk of dementia [28]. At age 85 years and older, low SBP predicts the onset of dementia [15] and is associated with worse cognitive function [17].

Similarly, a cohort of male participants whose SBP trajectories were followed over 32 years showed that those who develop dementia had a greater increase in SBP followed by a decrease in SBP compared to those who did not develop dementia [29]. These findings could explain the accelerated cognitive decline we found in our patients with low SBP under antihypertensive treatment. Our results are also in line with Mosello *et al.'s* findings [12] where 172 patients with a mean age of 79 years, taking antihypertensive therapy, and with a diagnosis of dementia or mild cognitive impairment of outpatient memory clinics were followed-up for a median of 9 months. Our results confirm and extend these findings by showing similar associations in a population-based cohort over a longer observation period of 5 years.

This cohort study has several strengths. The population-based sample included a large number of participants, extensive measurements and high follow up rates with a low risk for selection bias. The inclusion of participants from nursing homes further enhances the generalisability of the findings.

This is an observational study, with all the limitations that implies. However, it is useful to look at the associations we identified by situating them within the GRADE framework and apply the Bradford Hill's criteria for causation because 'observational studies may provide more relevant information than RCTs' [30]. The strength of association we found, consistency with prior studies, and the dose-response relationship in our study are three of these criteria. In addition, this study established a temporal relationship between SBP values measured at baseline and outcome assessments over 5 years. Our sensitivity analysis showed robust results when we excluded deaths within 1 year after baseline, which reduces, but does not exclude, the risk that our findings are due to reverse causality.

We acknowledge further limitations. First, there was no SBP measurement at baseline for about 5% of participants. Excluding these participants is unlikely to introduce bias as the numbers are small. Second, the risk for confounding by indication limits the causal interpretation of our associations. Interpretation of the results is helped by the findings of a large international study including >2500 GPs [31], which may allow us to understand and adjust for factors (for example frailty) that influence GPs' decision to start or not start antihypertensive therapy in the oldest-old. Third, if participants are prescribed with antihypertensive therapy but did not adhere to treatment, misclassification bias could be introduced. However, Dutch individuals seem to adhere best to therapy compared to seven other countries [32], and this high level of adherence reduces the risk of such bias in our sample.

Despite these limitations, the finding that low SBP is associated with increased mortality and cognitive decline in oldest-old under antihypertensive therapy is concerning. For clinicians, this study raises the question of what the optimal target blood pressure level is for 85-year-

oldm frail patients. We support the suggestions from Benetos *et al.* [33] to follow an individualized approach when treating hypertension in oldest-old >80 years with frailty, due to the lack of evidence [6, 34]. Observational studies remain at risk for bias (i.e. reverse causality, residual confounding), and the way to provide more evidence could be via deprescribing trials to test effectiveness and safety of lowering or removing antihypertensive therapy. The Dutch DANTE trial used this approach over a 16-week period in patients aged 75 and older with mild cognitive impairment [35]. In DANTE, deprescribing was not beneficial but was safe. Future studies should try to recruit patients that could benefit the most from deprescribing such as individuals with frailty and/or limited life expectancy.

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Appendix text – detailed plan of analysis

We assessed associations between exposure (level of SBP with/without antihypertensive therapy) and outcomes (all-cause mortality/annual change in cognitive function) over 5 years.

Missing data was handled two ways: 1) We excluded participants with missing information on baseline SBP (n=24, 4%) and potential confounders (n=3-20, 1%-3%, income was the variable with most [n=20] missing data). 2) We grouped participants who were unable to perform the hand grip strength test (n=35, 6%) in the group of lower than median hand grip strength.

Our descriptive analysis compared baseline characteristics in those with/without antihypertensive treatment. Chi-square tests were performed for categorical variables, t-tests or Wilcoxon rank-sum test for continuous data where appropriate.

In a crude regression model, SBP was first grouped into quintiles. Only participants from the two most extreme quintiles of lowest and highest SBP (<140 and >170 mmHg) were retained. Finally, we re-parameterized both exposure variables (SBP and antihypertensive therapy) into a new categorical variable, with four sub-categories (2 levels of SBP by 2 levels of treatment) so we could visually explore associations of both exposure variables and each outcome at once. We then presented all-cause mortality in crude Kaplan-Meier time-to-event curves for each of the four groups. Groups (SBP/treatment) were compared with log-rank tests. Next, we grouped SBP in 10mmHg units for all participants. We found no evidence for a significant departure from linear trend (tested with Likelihood ratio test [LRT]).

For all-cause mortality, we used Cox proportional hazards models with SBP as the exposure, testing separately for antihypertensive treatment (yes/no). We tested proportional hazard assumptions and they were all valid. We, a priori, chose sex, and CVD as confounders, and took a causal modelling approach to identify potential confounders to the association of SBP/ treatment and the outcomes: living situation, income, education, smoking status, diabetes, and depression (i.e. GDS-score). We calculated crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) and tested the later for multicollinearity. Interaction was only tested as pre-specified for frailty in a subgroup analysis.

Annual change in cognitive function was calculated as the median annual difference and inter-quartile range (IQR) in MMSE for each of the four groups. We then compared estimates and IQR for low and high SBP, using Wilcoxon rank-sum tests separately for participants with/without antihypertensive treatment. While this approach did not account for correlated data (i.e. multiple measurements per participant), we later used a mixed-effects linear regression models that account for the clustering within each participant as a random effect [25].

The models provided estimates for 'SBP', 'year' (of follow-up) and 'SBP * year'. The estimate for 'SBP' indicated the baseline difference in MMSE per 10mmHg lower SBP (presented in Table 3 as 'baseline difference'). The estimate for 'year' indicated the annual change in MMSE (presented in Table 3 as 'annual change'). The estimate for 'SBP * year' indicates the accelerated change in MMSE per year per 10mmHg lower SBP (presented in Table 3 as 'accelerated decline').

Subgroup analyses were performed for the second aim, to see if frailty modified the associations of SBP/treatment with the outcomes. We stratified both models for low/high hand grip strength to explore effect sizes and directions of effects. We tested for interaction using LRT. However, due to small sample sizes, this subgroup analysis was only exploratory.

A two-sided P-value of 0.05 was statistically significant. We used STATA 15.0 (StataCorp, College Station, TX, USA) for all analyses.

Appendix table 1. Subgroup of participants with baseline systolic blood pressure (SBP) at baseline of <140 mmHg (lowest quintile) and >170 mmHg (highest quintile) stratified by antihypertensive treatment (*n*=214).

Domains	Antihypertensive treatment		P-value[a]	No antihypertensive treatment		P-value[a]
	<140 mmHg (*n*=43)	>170 mmHg (*n*=44)		<140 mmHg (*n*=60)	>170 mmHg (*n*=67)	
Sociodemographic characteristics						
Women, n (%)	30 (69.8)	32 (72.7)	0.76	40 (66.7)	41 (61.2)	0.52
Low education[b], n (%)	26 (66.7)	31 (72.1)	0.59	39 (66.1)	45 (69.2)	0.71
Low income[c], n (%)	18 (47.4)	16 (37.2)	0.36	32 (54.2)	32 (50.0)	0.64
Institutionalized, (%)	13 (33.3)	2 (4.7)	0.001	23 (38.3)	6 (9.2)	<0.001
Cardiovascular characteristics						
Current Smoker, n (%)	2 (4.7)	8 (18.2)	0.089	9 (15.5)	12 (17.9)	0.81
Diabetes mellitus, n (%)	10 (25.6)	5 (11.6)	0.15	14 (23.3)	8 (12.3)	0.16
CVD[d], n (%)	33 (76.7)	26 (59.1)	0.078	25 (41.7)	29 (43.3)	0.86
Functional characteristics						
Cognition (MMSE [e]), median (IQR)	26 (19-27)	27 (23-28)	0.021	23.5 (13-27)	27 (23-28)	0.002
Depression (GDS[f]), median (IQR)	2 (1-4)	2 (1-3)	0.35	2 (1-4)	1 (1-3)	0.17
Low hand grip strength[g], n (%)	32 (74.4)	27 (61.4)	0.19	48 (80.0)	38 (56.7)	0.005

[a] P-values were derived from Chi-square tests for categorical variables, exact Fisher tests (if too few observations per cell expected), and Wilcoxon rank-sum test for continuous not-normally distributed data.

[b] defined as primary school only

[c] defined as state pension only (about EUR 750 monthly)

[d] CVD included angina pectoris, myocardial infarction, heart failure, intermittent claudication, peripheral arterial surgery, TIA, and stroke

[e] MMSE, possible scores range from 0 to 30 points (worst to best). Missing data in n=3.

[f] GDS-15, possible scores range from 0-15 (worst to best). Data not available for participants with Mini-Mental State Examination (MMSE) scores <18 (n=44).

[g] Participants unable to perform the test (n=16) were classified to have low hand grip strength.

Appendix table 2. Sensitivity analysis excluding participants that died within one year after baseline. Subgroup analysis for hand grip strength and associations of systolic blood pressure (SBP) and all-cause mortality per 10 mmHg lower SBP (n=534)

		Hazard ratio (95% CI) per 10 mmHg lower SBP	P-value
Treatment			
Overall[a] (n=235)		*1.25 (1.10, 1.42)*	*0.001*
By hand grip strength[b]	Low (n=150)	1.22 (1.05, 1.41)	0.009
	High (n=85)	1.28 (0.97, 1.67)	0.078
No treatment			
Overall[a] (n=299)		*1.09 (0.99, 1.19)*	*0.074*
By hand grip strength[b]	Low (n=184)	1.11 (0.99, 1.23)	0.069
	High (n=120)	0.99 (0.85, 1.17)	1.00

[a] Participants during and without antihypertensive treatment, adjusted for sex and cardiovascular disease

[b] Participants who were unable to perform the test (n=32) were classified to be low in hand grip strength, adjusted for sex and cardiovascular disease
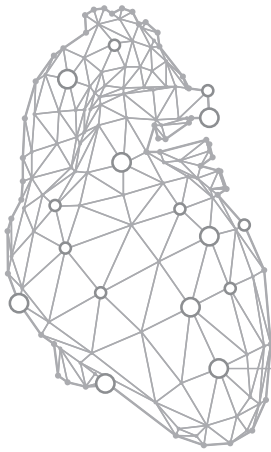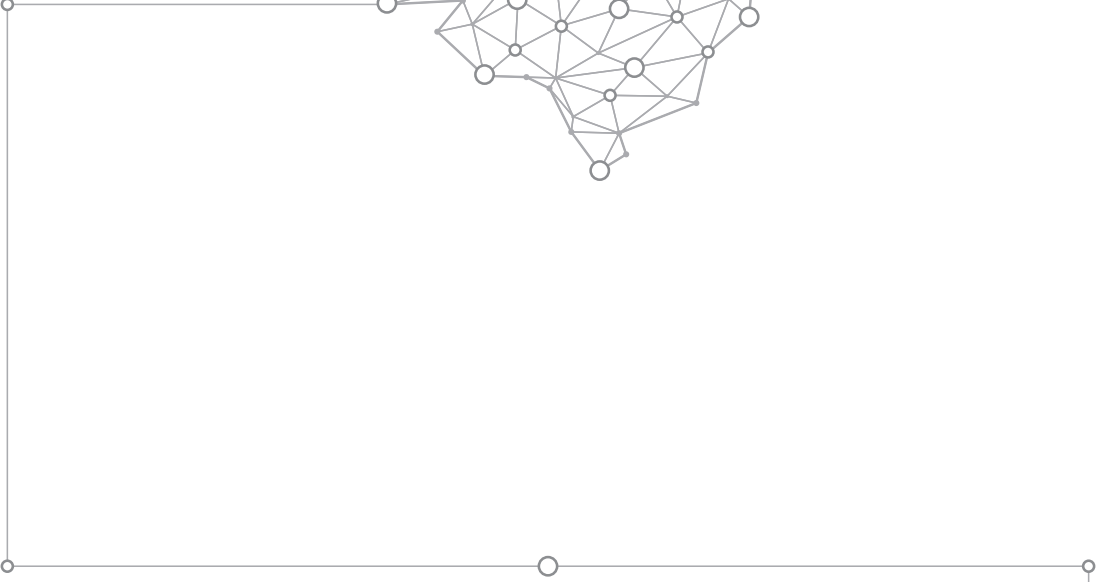
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Association of low systolic blood pressure under antihypertensive treatment and cognition in old age

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Jeanet W Blom, Jacobijn Gussekloo

ABSTRACT

Background/Objectives

Determine if systolic blood pressure (SBP) and antihypertensive treatment are associated with one-year changes in cognitive/daily functioning or quality of life (QoL) in older participants with/without complex health problems.

Design

Population-based prospective cohort with one-year follow-up.

Setting

Participants in the Integrated Systematic Care for Older Persons (ISCOPE) trial.

Participants

Primary care patients, eligible when ≥75 years and SBP recorded in electronic medical records one-year before baseline.

Measurements

Grouped participants into SBP categories (<130mmHg/130-150mmHg/>150mmHg) and antihypertensive treatment (yes/no). Used mixed-effects linear regression models to evaluate change from baseline to one-year follow-up in outcome measures (Mini Mental State Examination (MMSE), Groningen Activities Restriction Scale (GARS), and EQ-5D-3L). Adjusted models for age, sex, baseline values of MMSE/GARS/EQ-5D-3L and stratified for complex health problems.

Results

Participant (n=1,266) age averaged 82.4 (5.1) years; 874 were women (69.2%). In participants under antihypertensive therapy (1,057, 83.5%) with SBP<130mmHg, cognitive decline was 0.90 points in MMSE while in those with an SBP >150mmHg it was 0.14 (i.e. 0.76 less decline). In the multivariable model, cognitive decline was 1.01 (95%CI 0.47-1.55, P<0.001) when SBP was >150mmHg (P-for-trend<0.001). Complex health problems modified the association of SBP with cognitive function: the association was mainly seen in those with complex health problems (P-for-trend<0.001) and not in those without (P-for-trend=0.13). Daily functioning or QoL did not differ across strata of SBP and antihypertensive treatment.

Conclusions

Participants aged ≥75years under antihypertensive treatment with a SBP ≥130mmHg compared to <130 showed a significantly and clinically relevant benefit in cognition after one year, without loss of daily functioning or QoL. This effect was strongest in participants with complex health problems. For those, future trials should investigate if deprescribing is beneficial.

INTRODUCTION

In Western countries, hypertension is present in up to 30% of the population [1] and is a leading disability risk [2]. Its prevalence sharply increases with age [3], but for many years many physicians believed hypertension in old age was a healthy adaptation to arteriosclerotic rigidity [4] and did not treat patients >60 for hypertension [5]. In the 1990s, trials began to show that antihypertensive treatment reduced stroke and myocardial infarction in patients >60 [6-8], and physicians changed their practice. However, as populations "grey", definitions of "old" are shifting. Life expectancy has increased worldwide: people ≥75 years are now the fastest-growing age group; this population will triple within 35 years [9]. Some older individuals are very healthy, but others are frail and have two or more chronic conditions (multimorbidity) or other complex health problems [10].

Though updated guidelines recommend lowering blood pressure targets in older patients, cohort studies have raised concern that lowering SBP too much might harm them, by, for example accelerating cognitive decline [11-21]. A recent network meta-analysis of 17 hypertension trials proved the effectiveness and safety of lowering SBP to <130 mmHg in patients with hypertension [22], spurring the American College of Cardiology/American Heart Association Task Force (ACC/AHA) to update their guidelines. ACC/AHA recommends a target SBP of <130mmHg for non-institutionalized older patients [23]. Hypertension trials often exclude older, frail patients and those with complex health problems [24], so some have questioned the generalizability and applicability of the results of these studies of the general population, especially to older patients [25, 26]. An observational study of 172 patients (mean age 79 years) by Mosello *et al.* found low SBP and cognitive decline were associated in patients with dementia or mild cognitive impairment (MCI) under antihypertensive treatment, but not in untreated patients [27]. This study concluded that optimal SBP in those patients was between 130 and 145 mmHg, since lowering target values might further impair cognitive function, and was the only study that analysed patients under antihypertensive treatment separately from patients without treatment.

We set out to determine if low SBP and cognitive decline were similarly associated in a larger cohort of Dutch community-dwelling older participants under antihypertensive treatment and without. We also tested for an association between SBP and daily functioning and quality of life (QoL). We hypothesized these associations would be strongest in older participants with complex health problems.

METHODS

Design

This is a prospective cohort study based on data from the Integrated Systematic Care for Older Persons (ISCOPE) study, a cluster-randomized trial.

ISCOPE trial

The ISCOPE study included participants from 2009 to 2010 in Leiden, the Netherlands [28]. 560 general practitioners (GPs) were invited, and, of these, 104 (19%) invited their patients to participate. In the Netherlands, every person is registered at a GP practice. Inclusion criteria were age ≥75 years; terminal illness or life expectancy of <3 months were the only exclusion criteria. Participants were randomized to either an integrated care plan with a functional geriatric approach or usual care [28]. Of 11,476 patients in the target population, 7,285 (63.4%) answered a screening questionnaire. We selected a random sample of 1,921 to follow up for one year. Of these, 106 (5.5%) participants died; mortality risk was the same in intervention and control groups (P=0.48).

Study population and eligibility criteria

We needed electronic medical records (EMR) data in order to extract SBP measurements and identify antihypertensive drugs from their Anatomical Therapeutic Chemical (ATC) codes. We thus selected participants based on four criteria: 1) they consented to allow us to analyse their EMR data; 2) we could link their EMR data to link the ISCOPE dataset; 3) they were selected for one year of follow-up in ISCOPE; and 4) their SBP measurements were recorded for the year before they were included in ISCOPE (Study flow chart in Figure 1).

Ethical approval

Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Ethics Committee of the Leiden University Medical Center, the Netherlands (P09.096) approved the ISCOPE study, registered in the Netherlands Trial Register (NTR1946).

Exposures

We averaged SBP values from EMR of up to five of the most recent measurements taken the year before baseline. We grouped participants, based on mean SBP, into 3 categories (<130 mmHg, 130-150 mmHg, and >150 mmHg). Those with SBP <130mmHg were the reference group. We used EMR data at baseline to determine if participants were under antihypertensive treatment or not.
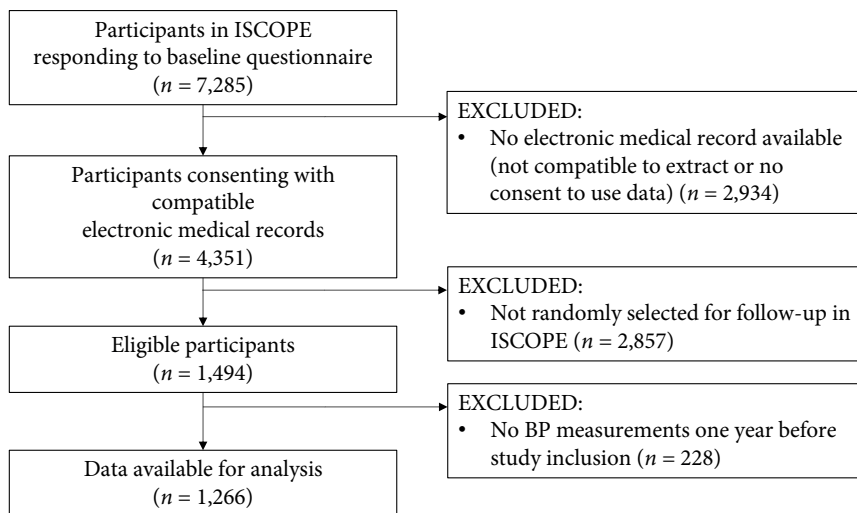
Figure 1. Study flow chart

Outcome measurements

In ISCOPE, research nurses made home visits at baseline and at one-year follow-up [28]. The MMSE measures cognitive function on a scale of 0-30 points (higher scores indicate better function) [29]. The GARS questionnaire measures basic and instrumental activities of daily living. The combined score ranges from 18-72 points (higher score indicates greater disability [30]). QoL was assessed with EQ-5D-3L index values: participants rated their health status in 5 dimensions (mobility; self-care; usual activities; pain and discomfort; anxiety and depression), and at three levels (no, some, or extreme problems) [31], and we converted them to a weighted index, based on the EuroQoL Group (full health has a value of 1, death, a value of 0) [32].

Confounders

We, *a priori,* chose age, sex, and either MMSE, GARS, or EQ-5D-3L at baseline, depending on the outcome as confounders. We took a causal modelling approach to identifying potential confounders of the association between SBP/treatment and our outcomes. We assessed the strength of confounding by examining change between our crude and adjusted models for each of the following covariates: living situation; income; education; diabetes; cardiovascular disease (CVD) (myocardial infarction, angina pectoris, intermittent claudication, other ischemic heart disease, stroke, TIA, or heart failure); and non-cardiovascular co-morbidities (cancer, diabetes, and depression). The final model included all variables a) considered to be confounders (change of +/-10% from crude model) or b) prespecified.

To identify participants with complex health problems, we used scores from a questionnaire that participants received at baseline. The questionnaire covered four domains (functional, somatic, mental, and social) [28], which each contained 4-9 questions. If participants reported problems in ≥2 questions in a domain, their score was 1 for that domain; if they reported no problems, it was 0. Participants that scored 1 in three or all domains, were classed as having complex problems.

Statistical analysis

In descriptive analysis, we compared baseline characteristics of participants with/without SBP measurements in the EMR to determine selection bias, then we compared participants with and without antihypertensive treatment. We used the Chi2-test for categorical data, t-test for normally distributed data, and Wilcoxon ranksum test for not-normally distributed continuous data.

In a primary analysis, we assessed associations between SBP category (<130mmHg, 130-150mmHg, >150mmHg) stratified by antihypertensive therapy (yes or no) and change in function in old age (MMSE, GARS, EQ-5D-3L) from baseline to one-year follow-up. We estimated the change in function and 95% confidence intervals (CI) in a crude mixed-effects regression model that only accounted for the correlated nature of data of participants under antihypertensive treatment or not by the same GP. We calculated P for trend to test a linear trend across categories of SBP within both strata (antihypertensive therapy yes and no). We then adjusted the mixed-effects regression models for sex, age and baseline values of MMSE, GARS, or EQ-5D-3L, depending on the outcome, and estimated the change in function related to SBP <130mmHg (reference category). Linear assumptions were tested and valid for all outcomes.

We performed two sensitivity analyses for the primary analysis: 1) we restricted our analysis to participants with no history of CVD at baseline; and, 2) we included the ISCOPE trial arm as confounder, although the original ISCOPE trial did not show that the integrated care plan increased QoL or daily function or changed health care use.

In a secondary analysis, we took the same approach, but we stratified for participants with and without complex health problems.

A two-sided P-value of 0.05 was statistically significant. We used STATA 15.1 (StataCorp, College Station, TX, USA) for all analyses.

RESULTS

Of 7,285 participants who responded to the screening questionnaire in ISCOPE, we excluded 2,934 (40.3%) because they did not consent to providing a link to their EMR data or their EMR data could not be linked with ISCOPE data. Of the 4,351 who remained, 1,494 (34.3%) were followed-up for one year in ISCOPE. Of those, we excluded 228 (15.3%) because they had no SBP measurements recorded in EMR (flow chart in Figure 1). Those we excluded for lack of SBP measurements were healthier overall than the study participants; they had less CVD (21% vs. 40%, P<0.001), less antihypertensive therapy (49% vs. 84%, P<0.001), less diabetes (15% vs. 22%, P=0.030), lower GARS score (27 vs. 31, P<0.001), higher EQ-5D 0.81 vs 0.77, P<0.001), higher MMSE-score [28 (26-29) vs. 28 (27-29), P=0.019], and less complex health problems (39% vs. 53%, P>0.001) (Appendix table 1).

The final dataset comprised 1,266 participants. Most of them (83.5%) were under antihypertensive treatment for hypertension (Table 1). At baseline, the sociodemographic characteristics of participants under or not under antihypertensive treatment were similar, but participants under antihypertensive treatment more often had an SBP >150 mmHg (35 % vs. 23%; P=0.004), more CVD (48% vs. 4%; P<0.001), more diabetes (23% vs. 15%; P=0.013), higher GARS score (31 vs. 28, P=0.003) and lower QoL (EQ-5D 0.77 vs. 0.78, P=0.045).

Crude one-year changes in cognitive function, daily function and quality of life

Figure 2 displays the crude estimates of changes from baseline to one-year follow-up in cognitive function (Panel A), daily functioning (Panel B), and QoL (Panel C). In participants under antihypertensive treatment, we found a clear trend across categories of SBP: with lower SBP, cognitive decline worsened (measured by MMSE) after one-year follow-up (P for trend 0.013). In participants under antihypertensive treatment and SBP <130mmHg, cognitive decline in one year averaged 0.90 points (95%CI 0.43-1.36) in MMSE, while it was 0.14 (95%CI 0.21-0.49) in those with SBP >150mmHg (0.76 points less decline in MMSE in participants with an SBP >150mmHg than in those with SBP <130mmHg). In participants without antihypertensive treatment, we observed a similar trend but it was not statistically significant (1.75 points, 95%CI 0.80-2.70 if SBP<130mmHg vs. 0.54 points, 95%CI 0.43-1.41 if SBP>150mmHg; P for trend 0.08).

We found no association between SBP and daily functioning or QoL in participants under or not under antihypertensive therapy.

Multivariable models for cognitive function, daily functioning and QoL

Table 2 displays the changes in function among the reference group (<130mmHg) stratified by antihypertensive treatment for each outcome, separately (MMSE, GARS, EQ-5D-3L).

Table 1. Baseline characteristics of participants overall and grouped by antihypertensive treatment (n=1,266)

	Overall (n=1,266)	Antihypertensive treatment		P-value[a]
		Yes (n=1,057)	No (n=209)	
Sociodemographic data				
Female, n (%)	874 (69)	728 (69)	146 (70)	0.72
Age, years (SD)	82.4 (5)	82.5 (5)	82.3 (5)	0.59
Primary school only, n (%)	656 (52)	541 (52)	115 (55)	0.33
Low income[b], n (%)	197 (16)	166 (16)	31 (15)	0.72
Residential home, n (%)	101 (8)	83 (8)	18 (9)	0.72
Systolic blood pressure, n (%)				
<130 mmHg	237 (19)	197 (19)	40 (19)	
130-150 mmHg	613 (48)	493 (47)	120 (57)	0.004
>150 mmHg	416 (33)	367 (35)	49 (23)	
Comorbidities, n (%)				
Cardiovascular disease (CVD)[c]	511 (40)	503 (48)	8 (4)	<0.001
Diabetes mellitus	274 (22)	242 (23)	32 (15)	0.013
Depression	182 (15)	148 (14)	34 (16)	0.42
Cancer	159 (13)	134 (13)	25 (12)	0.75
Baseline function, median (IQR[d])				
MMSE[e] score	28 (26-29)	28 (26-29)	28 (26-29)	0.99
GARS[f] score	31 (24-39)	31 (24-40)	28 (22-36)	0.003
EQ-5D-3L[g] index values	0.77 (0.57-0.84)	0.77 (0.51-0.84)	0.78 (0.65-0.89)	0.045
Complex health problems[h]	674 (53)	571 (54)	103 (50)	0.23

[a] P-value from chi-square test for categorical data; t-test for normally-distributed continuous data, Wilcoxon ranksum test for not normally-distributed continuous data

[b] defined as state pension only (about EUR 750 monthly)

[c] CVD included myocardial infarction, angina pectoris, intermittent claudication, other ischemic heart disease, stroke, TIA, and heart failure

[d] IQR = inter quartile range

[e] Mini-Mental State Examination (MMSE) on a scale of 0-30 points (higher scores indicate better cognitive function)

[f] Groningen Activities Restriction Scale (GARS); the score ranges from 18 to 72 (higher scores indicate greater disability)

[g] Quality of life (EQ-5D-3L index values; full health has a value of 1, dead a value of 0)

[h] Defined as patients having problems in three or more of four domains (functional, somatic, mental, and social)

Compared to the reference group, participants under antihypertensive therapy showed less cognitive decline after one year by 0.71 points in MMSE (95%CI 0.20-1.22, P=0.007) when SBP was 130-150mmHg and by 1.01 points in MMSE (95%CI 0.47-1.55, P<0.001) when SBP was >150mmHg (P for trend <0.001). In participants not under antihypertensive therapy, the trend was in the same direction but not significant (P for trend 0.07).
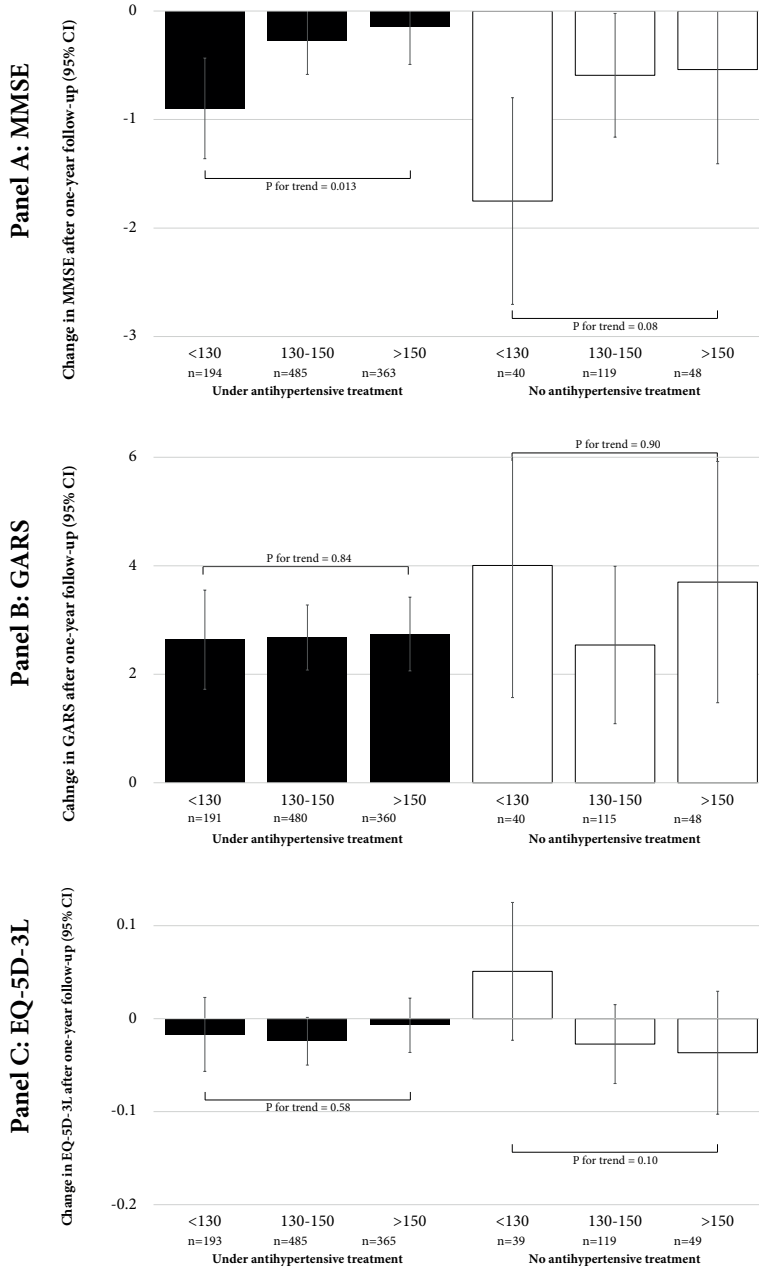
Figure 2. Associations of systolic blood pressure, antihypertensive treatment, and change in function after a one-year follow-up. Estimates, 95% CI and p-for trend from crude mixed-effects linear regression accounting for clustering within general practitioners. Panel A: cognitive function measured by Mini Mental State Examination (MMSE), (less points = cognitive decline); Panel B: daily functioning measured by Groningen Activities Restriction Scale (GARS), (more points = more disability); Panel C: Quality of life measured by EQ-5D-3L, (less points = lower quality of life).

Table 2. Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up (n=1,266). Multivariable mixed-effects regression model adjusted for age, sex, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

| | Antihypertensive treatment | | | | | | | |
| | Yes (n=1,057) | | | | No (n=209) | | | |
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	194	*Ref.*	-	<0.001	40	*Ref.*	-	0.07
130-150 mmHg	485	0.71 (0.20, 1.22)	0.007	-	118	1.04 (-0.04, 2.12)	0.06	-
>150 mmHg	362	1.01 (0.47, 1.55)	<0.001	-	48	1.22 (-0.03, 2.47)	0.06	-
Daily function								
<130 mmHg	191	*Ref.*	-	0.47	40	*Ref.*	-	0.70
130-150 mmHg	480	-0.08 (-1.11, 0.96)	0.88	-	114	-1.73 (-4.54, 1.10)	0.42	-
>150 mmHg	359	-0.37 (-1.47, 0.74)	0.51	-	48	-0.75 (-4.02, 2.52)	0.65	-
Quality of life								
<130 mmHg	193	*Ref.*	-	0.17	39	*Ref.*	-	0.14
130-150 mmHg	484	0.00 (-0.04, 0.04)	0.98	-	118	-0.06 (-0.14, 0.02)	0.13	-
>150 mmHg	364	0.03 (-0.02, 0.07)	0.24	-	49	-0.07 (-0.16, 0.02)	0.12	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 1.01 (95% CI 0.47 to 1.55) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

For the outcomes of daily functioning and QoL, there was no association between SBP category and change in GARS or EQ-5D-3L in either strata (antihypertensive therapy yes/no).

Sensitivity analyses

The findings remained robust when we restricted the sample to participants with no history of CVD at baseline (Appendix table 2). When we added the ISCOPE trial arm to which participants were allocated our estimates remained the same (data not shown).

Secondary analysis for complex health problems

In participants with complex health problems (n=674, 53%, Table 3), we found the same association. Compared to the reference group (SBP<130mmHg), participants showed less cognitive decline after one year by 0.99 points in MMSE (95%CI 0.32-1.66, P=0.004) when SBP was 130-150mmHg and by 1.39 points in MMSE (95%CI 0.68-2.11, P<0.001) when SBP was >150mmHg (P for trend <0.001). This association was not found in participants without complex health problems (P for trend 0.35, Appendix table 3). Complex health problems did not modify the effect on daily functioning or QoL.

Table 3. Subgroup analysis restricted to patients with complex health problems (n=674). Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up (n=1,266). Multivariable mixed-effects regression model adjusted for sex, age, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

| | Antihypertensive treatment | | | | | | | |
| | Yes (n=571) | | | | No (n=103) | | | |
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	117	*Ref.*	-	<0.001	20	*Ref.*	-	0.13
130-150 mmHg	258	0.99 (0.32, 1.66)	0.004	-	60	1.90 (0.05, 3.75)	0.044	-
>150 mmHg	189	1.39 (0.68, 2.11)	<0.001	-	22	1.78 (-0.42, 3.98)	0.11	-
Daily function								
<130 mmHg	115	*Ref.*	-	0.59	20	*Ref.*	-	0.65
130-150 mmHg	254	-0.18 (-1.57, 1.20)	0.79	-	57	-2.02 (-6.14, 2.10)	0.34	-
>150 mmHg	188	-0.40 (-1.88, 1.09)	0.60	-	22	-1.20 (-6.11, 3.72)	0.63	-
Quality of life								
<130 mmHg	117	*Ref.*	-	0.61	19	*Ref.*	-	0.19
130-150 mmHg	257	-0.03 (-0.08, 0.03)	0.21	-	60	-0.11 (-0.23, 0.01)	0.08	-
>150 mmHg	190	0.01 (-0.05, 0.07)	0.99	-	22	-0.10 (-0.24, 0.04)	0.16	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 1.39 (95% CI 0.68 to 2.11) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

DISCUSSION

In this large Dutch primary care cohort of older persons with a follow-up of one year, those under antihypertensive treatment had less cognitive decline if their SBP in the year before baseline was ≥130 mmHg. The association between higher SBP and less cognitive decline in participants under antihypertensive treatment was strongest seen in those with complex health problems. Daily functioning and QoL were the same across strata of SBP and antihypertensive treatment. Sensitivity analyses that excluded participants with CVD or that included the trial arm of the ISCOPE trial in the model supported these findings.

Interpretation and scientific context

Our study builds on Mosello *et al.* [27], but is much larger (1,266 vs. 172 participants), and was conducted in a different setting (general practice vs outpatient memory clinics). Mosello *et al.* included only patients with dementia or mild cognitive impairment. Our study included participants often excluded from trials because they are sicker and have complex health problems. We found the same associations, but also demonstrated that complex health problems

changed the association. This finding lines up with other studies that found associations changed with frailty [33, 34]. Studies of older patients that did not stratify on antihypertensive treatment, found either no association [35] or an association between higher SBP, better cognition, and lower risk of dementia [36]. Our study helps explain this difference by showing that, in participants without complex health problems, low SBP is not as clearly associated with cognitive decline [37] as in those with complex health problems.

Less cognitive decline by 1.39 points in MMSE (95%CI 0.68-2.11) than the reference group (SBP<130 mmHg) is a clinically meaningful difference: this difference of 1.39 MMSE points is greater than the average annual decline in MMSE in those aged 85 [12].

At the same time, we found no evidence SBP was associated with changes in daily function under antihypertensive therapy, though prior studies identified both positive and negative associations [13, 38, 39]. A cohort study of 35 centenarians in Poland found higher SBP benefitted daily activity after follow-up [13]. The Leiden-85-plus study found higher SBP levels were associated with lower ADL disability over 5 years [38]. In contrast, a US longitudinal cohort study of about 600 75-year-olds found high SBP was associated with declining physical function (measured by gait speed) over 10 years of follow-up [39]. This diametric association might be explained by age: there was evidence that high SBP was associated with physical function at age 75, but that high SBP increased physical function in those >85 and >100. Most studies that assessed the association between SBP and function in old age did not assess QoL. A Polish study of about 11,500 old patients found that those treated for hypertension (especially those on multiple antihypertensive medications) had optimal QoL with higher SBP [40], but our results suggest no association between SBP and one-year change in daily function or QoL.

Strengths and limitations

Strengths of our study are the high number of older participants recruited by a large group of GPs, and the extensive measurements that take into account cognitive function, daily functioning, and QoL. Our study has the following limitations. It was observational, so we cannot exclude residual confounding, but the strength of the associations we identified, consistency with prior studies, dose-response relationship, and temporal relationship of SBP measurements and outcome assessments all point towards a causal interpretation. Although the participants we excluded because they had no SBP measurements recorded in the last year before the start of the study were healthier, they did otherwise not differ from responders. This last limitation can also be considered a strength, since we included sicker, older participants with a high proportion of CVD under antihypertensive treatment, and this ever-increasing group is often excluded from trials.

Implications

If higher blood pressure under treatment is better for cognitive function, then it might benefit patients to increase their blood pressure by deprescribing antihypertensive treatment. Early trials like the Dutch DANTE study asked if deprescribing antihypertensive medication improved cognitive function in older patients with mild cognitive impairment but found no evidence of effect after 16 weeks of follow-up [41]. The long term effects of deprescribing antihypertensives are still uncertain, but a recent Cochrane review found withdrawing from antihypertensive therapy in old age did not increase mortality [42]. We encourage researchers to conduct new randomized trials to test the long-term effectiveness and safety of deprescribing antihypertensive therapy to raise SBP, especially in individuals with complex health problems.

Until the results of these new trials are available, clinicians must daily decide on appropriate treatment for hypertension in older patients with limited evidence, including this study [25, 26]. Antihypertensive treatment is intended to reduce the risk of cardiovascular events and to preserve cognitive/daily function and QoL in older people. But our results show that SBP <130 mmHg under antihypertensive treatment is associated with additional cognitive decline. Our results suggest SBP thresholds for treatment should be redefined, especially for older persons with complex health problems. A more individualized approach might be best right now [43]. Since older patients are more likely to have complex problems and suffer accelerated cognitive decline, clinicians are advised to be cautious about lowering SBP too much.

Conclusions

In our study in the primary care setting, older participants aged ≥75 years under antihypertensive treatment with an SBP ≥130 mmHg showed significant and clinically relevant benefit in cognitive function after one year compared to participants whose SBP was <130mmHg, without loss to either daily functioning or QoL. A similar, but not significant trend was seen in participants not under antihypertensive treatment. This effect was strongest in participants with complex health problems under antihypertensive treatment. A more individualized approach to treat hypertension in older patients with complex health problems might be best right now until deprescribing trials could test if deprescribing antihypertensive treatment is beneficial or not.

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Appendix table 1. Baseline characteristics of participants with and without blood pressure measurements 1 year prior to study inclusion (*n*=1,494).

| Domains | Overall (n = 1,494) | Blood pressure measurements 1 year before study inclusion | | P-value[a] |
		Yes (n = 1,266)	No (n = 228)	
Sociodemographic data				
Female, n (%)	1,018 (68)	874 (69)	144 (63)	0.074
Age, years (SD)	82.3 (5)	82.4 (5)	81.4 (5)	0.006
Primary school only, n (%)	768 (52)	656 (52)	112 (49)	0.43
Low income[b], n (%)	225 (15)	197 (16)	28 (12)	0.20
Residential home, n (%)	124 (8)	101 (8)	23 (10)	0.29
Comorbidities, n (%)				
Cardiovascular disease (CVD)[c]	554 (37)	506 (40)	48 (21)	<0.001
Under antihypertensive therapy	1,168 (78)	1,057 (84)	111 (49)	<0.001
Diabetes mellitus	309 (20)	274 (22)	35 (15)	0.030
Depression	209 (14)	182 (15)	27 (12)	0.30
Cancer	186 (13)	159 (13)	27 (12)	0.76
Baseline function, median (IQR[d])				
MMSE[e] score	28 (26-29)	28 (26-29)	28 (27-29)	0.019
GARS[f] score	30 (24-39)	31 (24-39)	27 (21-34)	<0.001
EQ-5D-3L[g] index values	0.78 (0.60-0.84)	0.77 (0.57-0.84)	0.81 (0.67-0.89)	<0.001
Complex health problems[h]	764 (51)	674 (53)	90 (39)	<0.001

[a] P-value from chi-square test for categorical data; t-test for normally-distributed continuous data, Wilcoxon ranksum test for not normally-distributed continuous data

[b] defined as state pension only (about EUR 750 monthly)

[c] CVD included myocardial infarction, angina pectoris, intermittent claudication, other ischemic heart disease, stroke, TIA, and heart failure

[d] IQR = inter quartile range

[e] Mini-Mental State Examination (MMSE) on a scale of 0-30 points (higher scores indicate better cognitive function)

[f] Groningen Activities Restriction Scale (GARS); the score ranges from 18 to 72 (higher scores indicate greater disability)

[g] Quality of life (EQ-5D-3L index values; full health has a value of 1, dead a value of 0)

[h] Defined as patients having problems in three or more of four domains (functional, somatic, mental, and social)

Appendix table 2. Subgroup analysis restricted to patients without history of cardiovascular disease (n=755). Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up. Multivariable mixed-effects regression model adjusted for age, sex, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

	Antihypertensive treatment							
	Yes (n=554)				No (n=201)			
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	83	*Ref.*	-	0.031	39	*Ref.*	-	0.07
130-150 mmHg	249	0.79 (0.15, 1.57)	0.046	-	113	1.07 (-0.03, 2.17)	0.06	-
>150 mmHg	214	0.98 (0.18, 1.77)	0.017	-	47	1.22 (-0.03, 2.52)	0.06	-
Daily function								
<130 mmHg	81	*Ref.*	-	0.76	39	*Ref.*	-	0.72
130-150 mmHg	248	-0.27 (-1.79, 1.25)	0.73	-	108	-1.69 (-4.61, 1.22)	0.26	-
>150 mmHg	214	-0.29 (-1.86, 1.28)	0.72	-	47	-0.73 (-4.08, 2.62)	0.67	-
Quality of life								
<130 mmHg	82	*Ref.*	-	0.08	38	*Ref.*	-	0.14
130-150 mmHg	250	0.02 (-0.04, 0.08)	0.49	-	112	-0.07 (-0.15, 0.01)	0.09	-
>150 mmHg	216	0.05 (-0.01, 0.11)	0.11	-	48	-0.08 (-0.17, 0.02)	0.11	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 0.98 (95% CI 0.18 to 1.77) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

Appendix table 3. Subgroup analysis restricted to patients without complex health problems (n=591). Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up (n=1,266). Multivariable mixed-effects regression model adjusted for sex, age, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.
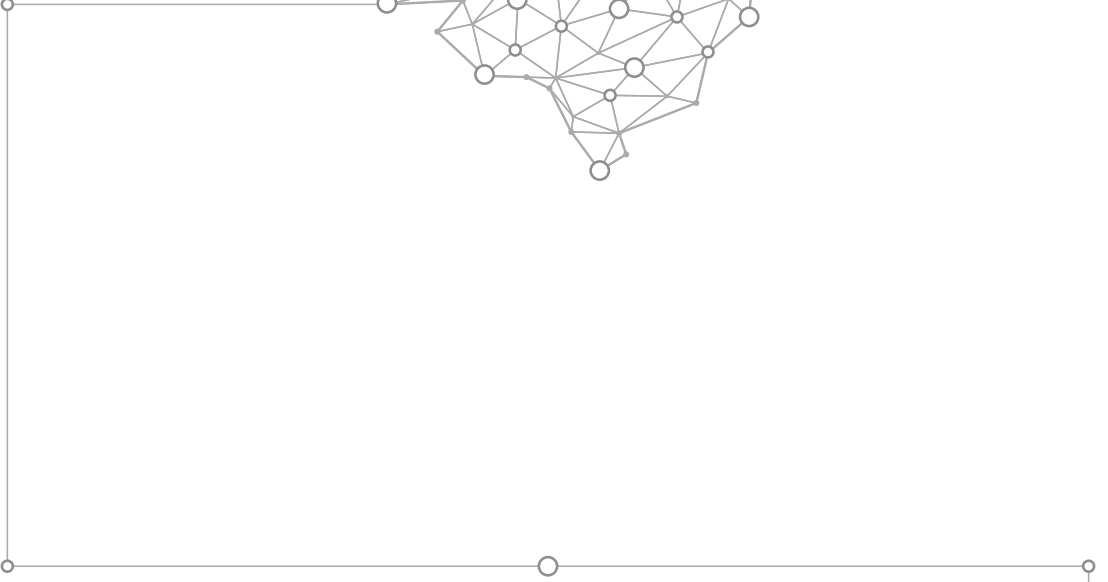
	Antihypertensive treatment							
	Yes (n=486)				No (n=105)			
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	77	*Ref.*	-	0.35	19	*Ref.*	-	0.15
130-150 mmHg	227	0.20 (-0.59, 0.99)	0.63	-	58	0.23 (-0.80, 1.25)	0.67	-
>150 mmHg	173	0.38 (-0.44, 1.20)	0.37	-	26	0.80 (-0.35, 1.96)	0.17	-
Daily function								
<130 mmHg	76	*Ref.*	-	0.56	19	*Ref.*	-	0.84
130-150 mmHg	226	-0.03 (-1.54, 1.60)	0.97	-	57	-2.07 (-5.92, 1.78)	0.29	-
>150 mmHg	171	-0.38 (-2.02, 1.25)	0.65	-	26	-0.77 (-5.06, 3.51)	0.72	-
Quality of life								
<130 mmHg	76	*Ref.*	-	0.35	19	*Ref.*	-	0.44
130-150 mmHg	227	0.03 (-0.03, 0.08)	0.36	-	58	0.02 (-0.08, 0.12)	0.7868	-
>150 mmHg	174	0.03 (-0.03, 0.09)	0.29	-	27	-0.04 (-0.15, 0.08)	0.52	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 0.38 (95% CI -0.44 to 1.20) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

5

Variation in GP decisions on antihypertensive treatment in oldest-old and frail individuals across 29 countries

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ABSTRACT

Background

In oldest-old patients (>80), few trials showed efficacy of treating hypertension and they included mostly the healthiest elderly. The resulting lack of knowledge has led to inconsistent guidelines, mainly based on systolic blood pressure (SBP), cardiovascular disease (CVD) but not on frailty despite the high prevalence in oldest-old. This may lead to variation how General Practitioners (GPs) treat hypertension. Our aim was to investigate treatment variation of GPs in oldest-olds across countries and to identify the role of frailty in that decision.

Methods

Using a survey, we compared treatment decisions in cases of oldest-old varying in SBP, CVD, and frailty. GPs were asked if they would start antihypertensive treatment in each case. In 2016, we invited GPs in Europe, Brazil, Israel, and New Zealand. We compared the percentage of cases that would be treated per countries. A logistic mixed-effects model was used to derive odds ratio (OR) for frailty with 95% confidence intervals (CI), adjusted for SBP, CVD, and GP characteristics (sex, location and prevalence of oldest-old per GP office, and years of experience). The mixed-effects model was used to account for the multiple assessments per GP.

Results

The 29 countries yielded 2,543 participating GPs: 52% were female, 51% located in a city, 71% reported a high prevalence of oldest-old in their offices, 38% and had >20 years of experience. Across countries, considerable variation was found in the decision to start antihypertensive treatment in the oldest-old ranging from 34-88%. In 24/29 (83%) countries, frailty was associated with GPs' decision not to start treatment even after adjustment for SBP, CVD, and GP characteristics (OR 0.53, 95%CI 0.48-0.59; ORs per country 0.11-1.78).

Conclusions

Across countries, we found considerable variation in starting antihypertensive medication in oldest-old. The frail oldest-old had an odds ratio of 0.53 of receiving antihypertensive treatment. Future hypertension trials should also include frail patients to acquire evidence on the efficacy of antihypertensive treatment in oldest-old patients with frailty, with the aim to get evidence-based data for clinical decision-making.

INTRODUCTION

Hypertension is the most important preventable cause of poor cardiovascular outcome and is responsible for disability and deaths from stroke, myocardial infarction and other diseases [1]. Treating hypertension is beneficial and (since the 1990s) it is known that treatment also reduces stroke rates and myocardial infarction in patients aged >60 years [2-4]. As life expectancy has increased worldwide, a new term was needed to describe those in the fastest-growing age group expected to triple within the next 35 years [5], i.e. the group 'oldest-old' is now defined as those aged >80 years.

The population of the oldest-old is heterogeneous. Some oldest-old are very healthy whereas others are multimorbid with complex problems. Although the group of multimorbid oldest-old is rapidly increasing, most trials still exclude them. Messerli *et al.* highlighted this commonly-applied exclusion by applying exclusion criteria taken from 13 hypertension trials with oldest-old participants, to a primary care cohort of hypertensive patients aged >60 years [6]: in this case, ≥70% of the oldest-old would have been excluded and they were both older and sicker.

The exclusion of such a large percentage of oldest-old has caused a serious gap in our knowledge and in guidelines to treat hypertension in patients with multimorbidity. Even more scarce are recommendations for frail patients: for example, of six current hypertension guidelines, only those of the European Society of Hypertension and of the European Society of Cardiology have a specific recommendation to leave decisions on antihypertensive therapy in the frail and oldest-old patients to the treating physician (class I C recommendation) [7].

Due to the current lack of clear evidence, the best management of hypertension in the oldest-old remains unknown; this may, in turn, lead to clinical variation. Although it is difficult to quantify, variation exists in the way that the best available evidence is applied in clinical practice [8]. Among the diverse reasons for this variation, the appropriateness of guidelines for physicians in treating specific groups of patients is of particular importance. However, to reduce clinical variation and improve quality of care/patient safety, there is a need to assess clinical variation among the oldest-old patients, who are consistently excluded from trials but suffer from both multimorbidity and frailty.

Therefore, the present study investigates clinical variation across countries of general practitioners' (GPs) decisions to start antihypertensive treatment in patients aged >80 years. Our hypothesis was that *frailty* would be an important factor in deciding *not* to start antihypertensive treatment in clinical practice, although this is not specifically addressed in most guidelines.

METHODS

Design

GPs from different countries were invited to participate in a survey based on case vignettes.

Setting

The aim was to recruit national representatives (defined as a GP in contact with a national GP network) of 40 countries on the European continent, and in Brazil and New Zealand. We also re-contacted six national representatives of GP networks participating in a previous survey [9]. Also invited to participate were: 1) national representatives of WONCA Europe (European Branch of the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians) [10]; 2) the European General Practice Research Network (EGPRN) [11]; and 3) the Network of Junior GPs in Europe (the Vasco da Gama Movement, VdGM) [12].

The study was conducted in accordance with the Declaration of Helsinki [13]. Because the responses of GPs were collected anonymously, most countries required no approval from an ethics committee. In countries where approval was mandatory (Switzerland, Brazil), a waiver from the ethics committee was obtained. In New Zealand, approval for the study was granted by the University of Auckland Ethics Committee.

Participants

All national representatives were asked to include as many GPs as possible from their GP network. Because primary care surveys usually score low on response rates, we regularly reported the numbers of participating GPs to the national coordinators, so they could send reminders if needed. The only inclusion criterion for the survey was to be actively working as a GP; this was asked at the beginning of the survey. Participants who did not meet this criterion (e.g. due to retirement) were excluded from completing the survey.

Procedures

Beforehand, we developed/tested the survey for optimal technicality between SurveyMonkey (www.surveymonkey.com, Palo Alto, CA, USA) and Stata, among five GPs. Then, to test for clarity/feasibility, the survey was piloted among a sample of 16 physicians working in Switzerland.

National representatives translated the survey from English to their own language. Finally, the survey was available in 21 languages. National representatives of Greece, Israel and Finland decided to distribute the survey in English. The correctness of all translations was evaluated by the team of collaborators.

First, we asked the GP's gender, office location (city, suburban, rural), and years of experience working as a GP (in 5-year bands). Second, GPs were asked to estimate the proportions of patients aged >80 years attending their GP office. Third, eight case vignettes were presented of oldest-old patients of both gender, presenting for a routine visit in a GP office without blood pressure-related symptoms and not receiving any antihypertensive treatment. For each case vignette, GPs were asked to decide if they would start antihypertensive treatment. All case vignettes differed in three primary characteristics: systolic blood pressure (SBP), cardiovascular disease (CVD), and frailty (Appendix table 1). SBP was either 140 mmHg or 160 mmHg. CVD was either present (e.g. case vignettes with a history of myocardial infarction or stroke) or absent. Because the condition of frailty lacks a common definition [14], we stated that frailty is defined as patients with at least two of the following criteria: unintentional weight loss, exhaustion, low level of activity, muscle weakness, and slow gait speed. Thus, a patient with a low level of activity and unintentional weight loss was considered to be frail. To facilitate filling in the survey, for each case vignette we indicated one of the following statements: "*You consider this patient to be frail*" or "*You don't consider this patient to be frail*".

The survey was distributed by email between March 9 and July 31 2016. As the only exception, Ukraine distributed the survey on paper during a regional GP meeting because there is insufficient internet access for GPs in Ukraine.

Statistical analysis

To describe baseline characteristics, proportions were calculated for dichotomized or categorized data, and means were calculated for continuous data.

To assess international variation in decisions for treatment, per country the crude proportions and confidence intervals (CI) were calculated for GPs who would start treatment.

To assess the role of frailty in the decision to start treatment per country, odds ratios (ORs) and CI were calculated per country using a mixed-effects model adjusted for GP's gender, years of experience, office location, prevalence of oldest-old in the GP practice, guideline compliance, SBP, and CVD. The mixed-effects model was used to account for the multiple assessments per GP. The estimate of each country was presented on a forest plot.

For each case vignette, we calculated the crude proportions of GPs starting treatment and also compared two corresponding case vignettes (e.g. in Case 1 the patient is not frail, whereas in Case 2 the patient is frail).

To assess the overall influence of SBP, CVD and frailty, the same mixed-effects model was used but, in addition, clustering within countries was taken into account.

A two-sided p-value of 0.05 was considered statistically significant. Analyses were performed with STATA 14.2 (StataCorp, College Station, TX, USA).

RESULTS

From March through July 2016, we contacted 40 national representatives from Europe, Brazil, Israel, Russia, and New Zealand and received replies from 29 countries. Overall, 13,671 GPs were invited, of whom 2,585 responded. Subsequently, 42 respondents were excluded because they were no longer working as a GP, resulting in 2,543 participants. The median response rate was 26% (IQR 10-62%) (Appendix table 2).

Table 1 presents the baseline characteristics of the participating GPs; 52.3% were female, 50.8% lived in a city, and 37.6% had >20 years of experience. The majority of GPs (61.3%) estimated the prevalence of the oldest-old patients in their practice to be >10%.

Table 1. Baseline characteristics of participating GPs from 29 countries.

Baseline characteristics (N=2,543)	n (%)
Female GP	1,341 (52.3)
Practice location	
City	1,292 (50.8)
Suburban	599 (23.6)
Rural	651 (25.6)
Experience as GP	
<5 years	471 (18.5)
5-10 years	445 (17.5)
11-15 years	341 (13.4)
16-20 years	328 (12.9)
>20 years	956 (37.6)
Self-estimated prevalence of patients >80 years at own practice	
<10%	851 (38.7)
10-20%	865 (39.4)
21-30%	323 (14.7)
>30%	159 (7.2)

Overall, the crude proportions of treatment varied considerably between countries (Figure 1). For example, the lowest proportion of treatment was found in the Netherlands (34.2%; 95% CI 32.0-36.5%) whereas Ukraine had the highest proportion (88.3%; 95% CI 85.3-90.9%).
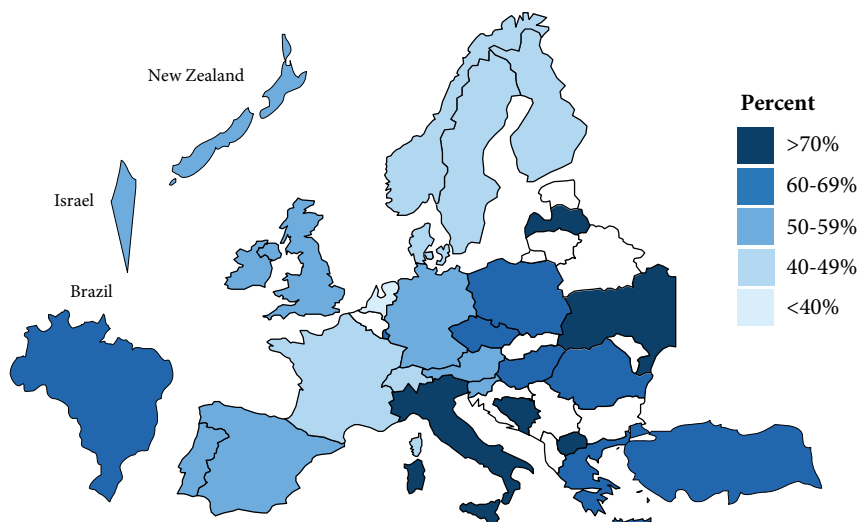
Figure 1. National percentages in which general practitioners decide to start antihypertensive treatment in all eight cases of oldest-old patients (unadjusted).

Figure 2 shows the GPs' treatment probability in frail oldest-old compared to non-frail oldest-old for each of the 29 countries. Overall, the treatment probability for all countries was OR 0.59 (95% CI 0.47-0.75) and the probability per country ranged from OR 0.11 in New Zealand to 1.78 in the Czech Republic. In 8/29 (28%) countries (i.e. New Zealand, Finland, Denmark, the Netherlands, Ireland, Switzerland, France and Israel) we are 95% confident that GPs would be less likely to start antihypertensive treatment in the frail oldest-old patients compared to the non-frail oldest-old patients. In 16/29 (55%) countries, an OR <1 was found but a 95% CI including 1; this larger 95% CI was due to the lower number of respondents per country (<30 per country in 45% of all countries). In 5/29 (17%) countries, the OR was >1 but (to a large extent) the 95% CI included 1.

GPs' decision to treat hypertension in the oldest-old varied considerably, ranging from 17.3% to 96.8% according to the specific case vignette (Table 2). The lowest level of treatment decision was scored in those case vignettes that included no frailty, no CVD, and a SBP 140 mmHg (17.3%; 95% CI 15.7-19.0%). The case vignettes that included CVD, SBP 160 mmHg and no frailty scored the highest (96.8%; 95% CI 95.9-97.5%). Besides frailty (adjusted OR 0.53; 95% CI 0.48-0.59), a SBP of 140 mmHg (adjusted OR 0.01; 95% CI 0.01-0.01) and no CVD (adjusted OR 0.29; 95% CI 0.26-0.32) were also independent factors that caused GPs not to start treatment.
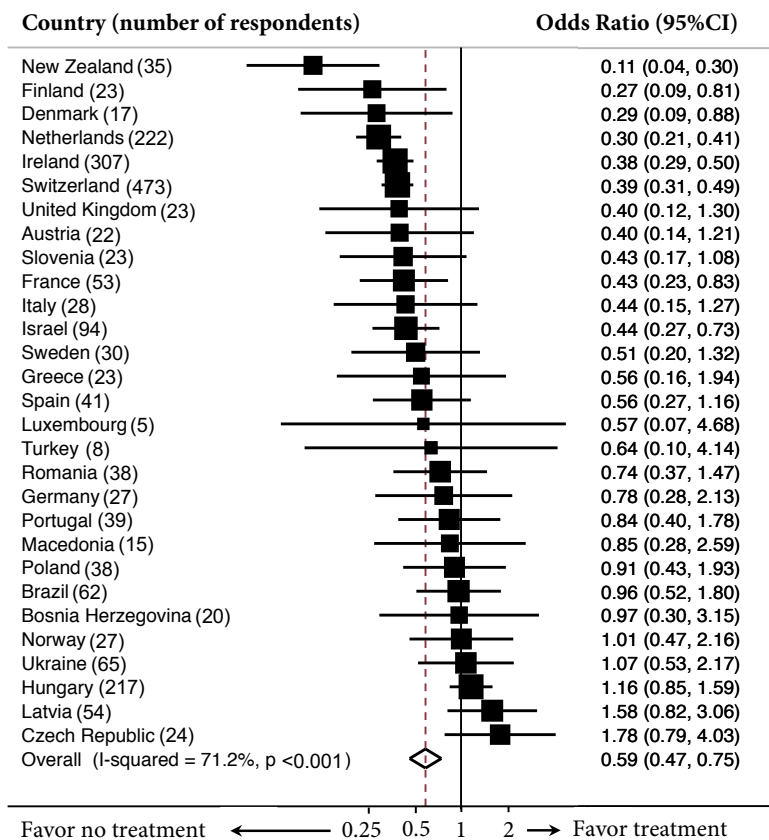
Country (number of respondents)	Odds Ratio (95%CI)
New Zealand (35)	0.11 (0.04, 0.30)
Finland (23)	0.27 (0.09, 0.81)
Denmark (17)	0.29 (0.09, 0.88)
Netherlands (222)	0.30 (0.21, 0.41)
Ireland (307)	0.38 (0.29, 0.50)
Switzerland (473)	0.39 (0.31, 0.49)
United Kingdom (23)	0.40 (0.12, 1.30)
Austria (22)	0.40 (0.14, 1.21)
Slovenia (23)	0.43 (0.17, 1.08)
France (53)	0.43 (0.23, 0.83)
Italy (28)	0.44 (0.15, 1.27)
Israel (94)	0.44 (0.27, 0.73)
Sweden (30)	0.51 (0.20, 1.32)
Greece (23)	0.56 (0.16, 1.94)
Spain (41)	0.56 (0.27, 1.16)
Luxembourg (5)	0.57 (0.07, 4.68)
Turkey (8)	0.64 (0.10, 4.14)
Romania (38)	0.74 (0.37, 1.47)
Germany (27)	0.78 (0.28, 2.13)
Portugal (39)	0.84 (0.40, 1.78)
Macedonia (15)	0.85 (0.28, 2.59)
Poland (38)	0.91 (0.43, 1.93)
Brazil (62)	0.96 (0.52, 1.80)
Bosnia Herzegovina (20)	0.97 (0.30, 3.15)
Norway (27)	1.01 (0.47, 2.16)
Ukraine (65)	1.07 (0.53, 2.17)
Hungary (217)	1.16 (0.85, 1.59)
Latvia (54)	1.58 (0.82, 3.06)
Czech Republic (24)	1.78 (0.79, 4.03)
Overall (I-squared = 71.2%, p <0.001)	0.59 (0.47, 0.75)

Favor no treatment ←——— 0.25 0.5 1 2 —→ Favor treatment

Figure 2. Influence of frailty on 2,053 general practitioners (GPs) when deciding to start antihypertensive treatment per country (adjusted).

Table 2. Percentages of general practitioners (GPs) starting antihypertensive treatment for the eight individual cases (n=2,053 GPs)

Cases	Proportion of GPs starting treatment	Case characteristics		
	% (95% CI)	Frailty	CVD	SBP 160 mmHg
Overall	**54.9 (54.1-55.7)**			
Case 1	17.3 (15.7-19.0)	–	–	–
Case 2	18.2 (16.6-20.0)	+	–	–
Case 3	85.4 (83.7-86.9)	–	–	+
Case 4	75.6 (73.6-77.5)	+	–	+
Case 5	96.8 (95.9-97.5)	–	+	+
Case 6	84.9 (83.2-86.4)	+	+	+
Case 7	32.5 (30.4-34.6)	–	+	–
Case 8	29.5 (27.5-31.6)	+	+	–

CVD=cardiovascular disease; SBP=systolic blood pressure

DISCUSSION

After sampling >2,500 GPs in 29 countries, this study revealed large clinical variation in starting antihypertensive treatment (ranging from 34-88%) based on case vignettes of oldest-old patients. As hypothesized, frailty proved to be an important patient characteristic for GPs in deciding whether or not to start antihypertensive treatment in 24/29 (83%) countries. The probability of a GP treating a frail patient was almost half that compared with a GP managing a non-frail patient. Current guidelines are clearer about the level of SBP related to initiating treatment; this was confirmed in the present study in which GPs were less inclined to start treatment in the case of SBP 140 mmHg compared to SBP 160 mmHg. Nevertheless, how to manage frailty will become increasingly important for an increasingly older and multimorbid population. When specific data from future trials that include frail patients become available, hypertension and other guidelines can be updated accordingly.

Scientific and Clinical Context of the Results

Treatment goals for hypertension are constantly changing [15]. Recent trials including oldest-old patients indicate aiming at the lower levels of SBP [3, 16]. However, these latter patients may differ from the general population that GPs are managing, due to the extensively applied exclusion criteria for the older and sicker patients [6]. Therefore, it remains unclear whether lowering SBP in multimorbid and frail patients does in fact lead to better outcomes. For example, in the SPRINT trial, frail patients showed smaller intertreatment group differences in SBP compared to non-frail patients, thus a lower SBP might be harder to achieve in frail patients [16]. On the other hand, there is evidence that frail oldest-old need a higher SBP. In a recent meta-analysis comparing pro- and retrospective cohort studies, Zhang *et al.* found that a higher SBP in frail oldest-old patients had a protective effect in lowering the risk of overall mortality [17]. Thus, current knowledge seems to be well summarized by Materson *et al.* who suggested to evaluate and treat frail oldest-old patients individually, while the healthier oldest-old should be treated regardless of their chronological age [18].

In the present study, this wide spectrum of recommendations and lack of clear evidence may partly explain the variation found between the participating countries. Differences in national guidelines/campaigns may have also led to differences between the countries. Nevertheless, this study confirmed our hypothesis that frailty is a factor that GPs take into consideration when starting antihypertensive treatment; moreover, we found that GPs were less likely to treat frail patients, even after adjusting for SBP and CVD. This is in line with findings from a Dutch qualitative study, where vulnerability was an important patient-related barrier for GPs when implementing guidelines for secondary cardiovascular prevention in oldest-old [19].

Interestingly, our findings share some findings and yet show difference with the only other published study on this topic. Mermans *et al.* conducted a similar survey among 305 GPs in Belgium. These authors also found large differences in treatment intentions for hypertension in the oldest-old patients between GPs and showed that there was a significant difference in the treatment intention of GPs between robust patients and strongly dependent patients. However, the stated that 'differences in the patients' level of dependency were not responsible for the variation in the overall treatment intention' [20]. However, on an international level, when including many countries, frailty was established as an important factor influencing GPs' treatment decisions.

Strengths and limitations

A strength of this study is the high number of countries and relatively large number of respondents (thanks to collaboration with WONCA Europe, EGPRN, and VdGM). Further, the sampled GPs were experienced with treating oldest-old patients. The inclusion of many countries enabled to produce a detailed map of treatment decision-making in Europe and elsewhere. In addition, we could establish that, in most countries, frailty is associated with a lower intention to treat, even when taking SBP and cardiovascular comorbidity into account.

This study has several limitations. First, although we report what the GPs stated they would do, this is not necessarily the same as what they would actually do. However, given the realistic case descriptions and the anonymous nature of the survey, we are relatively confident that this limitation has not introduced a systematic bias. Second, the response rate varied considerably between countries and the median rate was only 26%; this is a commonly occurring problem in primary care surveys [21]. However, our response rate was well within the range of other published survey among GPs in major journals [22]. Several reviews further noted that a low response rates in GP survey do not necessarily introduce selections bias [23, 24]. Third, in the case vignettes, only three patient characteristics were taken into consideration. However, because we focused on variation in treatment decision and the role of frailty in that decision, it was beyond the scope of this study to address all possible reasons related to GPs' treatment decision-making. Fourth, we mainly recruited one GP network per country, which is a selection of GPs dependent on their region of origin or area of interest; however, by adjusting our analysis for GP characteristics we aimed to take this possible confounder into account.

Implications

This study has several implications for research and clinical practice. First, the large variation in starting treatment in hypertensive oldest-old calls for high-quality cohort studies or (ideally) new hypertension trials specifically including frail patients to acquire evidence as to whether frailty is indeed an important factor when treating hypertension in oldest-old patients. Second, future studies should investigate whether treatment variation might be explained by e.g.

the recommendations in guidelines that individual GPs follow. Third, qualitative studies could help us to understand more of the variation we have found. If reasons for the international variation in treatment are established, educational campaigns can be launched to unify the quality of care in Europe (and elsewhere) based on the current body of evidence. Finally, future hypertension guidelines should stratify their recommendations not only for age, blood pressure level and cardiovascular comorbidity, but also for frailty.

Conclusions

In Europe, Brazil, Israel and New Zealand, GPs' decisions concerning starting antihypertensive treatment in the oldest-old varied considerably. Independently, the frail oldest-old patients had an almost 50% lower probability for their GP to consider them eligible to receive antihypertensive treatment. Future hypertension trials should also include frail patients to acquire evidence on the efficacy of antihypertensive treatment in oldest-old patients with frailty, with the aim to support and unify clinical decision-making.

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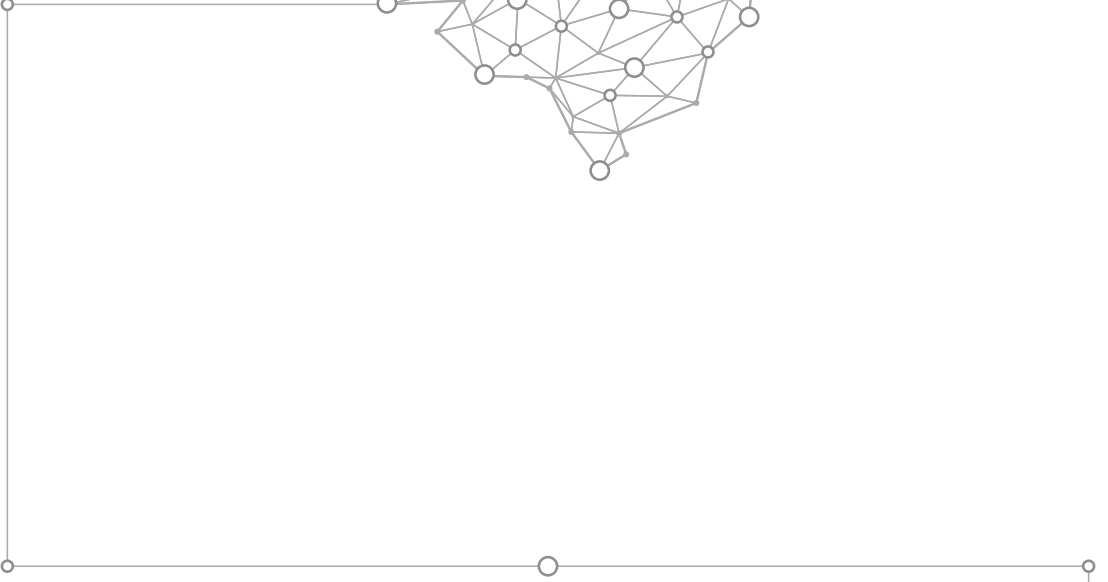
Appendix table 1. Characteristics of the eight case vignettes used in this survey

Cases	Frailty	Cardiovascular disease	Systolic blood pressure (mmHg)
Case 1	No	No	140
Case 2	Yes	No	140
Case 3	No	No	160
Case 4	Yes	No	160
Case 5	No	Yes	160
Case 6	Yes	Yes	160
Case 7	No	Yes	140
Case 8	Yes	Yes	140

All patients were aged >80 years and presented at the GP's office for routine control. None of the patients had blood pressure-related complaints and none was receiving any antihypertensive treatment.

Appendix table 2. Participating countries: number of invited GPs and response rates per country.

Country	Invited (n=13,671)	Participated (n=2,543)	Response rate (%)
Austria	549	28	5
Bosnia Herzegovina	260	26	10
Brazil	67	63	94
Czech Republic	356	27	8
Denmark	203	22	11
Finland	118	24	20
France	150	63	42
Germany	300	29	10
Greece	89	23	26
Hungary	515	332	64
Ireland	2576	401	16
Israel	395	140	35
Italy	120	38	32
Latvia	990	88	9
Luxembourg	40	7	18
Macedonia	28	21	75
Netherlands	1720	239	14
New Zealand	1524	39	3
Norway	99	31	31
Poland	79	69	87
Portugal	82	51	62
Romania	53	45	85
Slovenia	312	24	8
Spain	411	57	14
Sweden	130	34	26
Switzerland	1756	510	29
Turkey	648	17	3
Ukraine	73	69	95
United Kingdom	28	26	93
Median (IQR)			**26 (10-62)**

6

Burden of cardiovascular disease across 29 countries and GPs' decision to treat hypertension in oldest-old

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ABSTRACT

Objectives

We previously found large variations in general practitioner (GP) hypertension treatment probability in oldest-old (>80 years) between countries. We wanted to explore whether differences in country-specific cardiovascular disease (CVD) burden and life expectancy could explain the differences.

Design

Survey study using case-vignettes of oldest-old patients with different comorbidities and blood pressure levels. An ecological multilevel model analysis was performed.

Setting

GP respondents from European General Practice Research Network (EGPRN) countries, Brazil and New Zeeland.

Subjects

2,543 GPs from 29 countries

Main outcome measures

GP treatment probability to start or not start antihypertensive treatment based on responses to case-vignettes. Either low (<50% started treatment) or high (≥50% started treatment). CVD burden defined as ratio of disability-adjusted life years (DALYs) lost due to ischemic heart disease and/or stroke and total DALYs lost per country. Life expectancy at age 60 and prevalence of oldest-old per country.

Results

Of 1,947 GPs (76%) responding to all vignettes, 787 (40%) scored high treatment probability and 1160 (60%) scored low. GPs in high CVD burden countries had higher odds of treatment probability (OR 3.70; 95%CI 3.00-4.57); in countries with low life expectancy at 60, CVD was associated with high treatment probability (OR 2.18, 95%CI 1.12-4.25); but not in countries with high life expectancy (OR 1.06, 95%CI 0.56-1.98).

Conclusion

GPs' choice to treat/not treat hypertension in oldest-old was explained by differences in country-specific health characteristics. GPs in countries with high CVD burden and low life expectancy at age 60 were most likely to treat hypertension in oldest-old.

INTRODUCTION

In the Global Burden of Disease (GBD) study (2015), elevated blood pressure was among the leading risk factors for disability-adjusted life years (DALYs) [1]. Globally, about 10% of all DALYs are lost due to hypertension. To improve management of hypertension, the Lancet Commission issued a 10-point action plan in which one of these points was to individualize antihypertensive treatment according to cardiovascular risk, cultural differences, age, etc. [2].

The group of the oldest-old (patients aged >80 years) is both the fastest growing and also the most heterogeneous age group [3]. Some are healthy with very few chronic conditions, whereas others are frail, have multimorbidity (≥ 2 chronic conditions), or other complex problems [4]. This heterogeneity makes it particularly challenging for general practitioners (GPs) to find the best strategy (with optimal benefit to risk ratio) when deciding whether or not elevated blood pressure should be treated in this group [5]. This clinical dilemma can lead to variation in treating hypertension in oldest-old [6-9].

In the ATTENTIVE study [10], a large variation was found in GPs' decision to start antihypertensive treatment in oldest-old. In that study, eight case vignettes of oldest-old were presented to >2,500 GPs from 29 (mainly) European countries and, for each case, they were asked whether or not they would start treatment. In the Netherlands, 34% of all cases would have been treated compared with 88% in Ukraine. Part of this variation was explained by the differences in patient characteristics, i.e. level of blood pressure, cardiovascular disease (CVD), and frailty. However, given the variation across countries, it seems feasible that country-specific health characteristics could explain part of the variation.

Therefore, the present study investigates whether country-specific health differences in CVD burden in older patients, and life expectancy at age 60 years, are related to GP treatment probability to start antihypertensive treatment. We hypothesized that there would be a positive association between CVD burden and GP treatment probability, but that life expectancy at age 60 years would modify that association.

METHODS

Design and Setting
This was an ecological study using a multilevel model. Aggregated country-specific data were used from publicly available sources (see section 'Variables') and individual-level data (level of GPs) were used from the *Antihypertensive TreaTmENT In Very Elderly* (ATTENTIVE)

study. In the ATTENTIVE study, GPs from 29 countries (including Brazil, Israel and New Zealand) were enrolled (March-July 2016) [10].

Ethical considerations

The ATTENTIVE study was conducted in compliance with the Declaration of Helsinki [11]. GPs provided informed consent by responding to the questionnaire. Since the participating GPs responded anonymously, no formal medical ethics approval was required from most of the countries. However, in Brazil and Switzerland the research ethics committees issued a waiver, and in New Zealand the research ethics committee of the University of Auckland approved this study.

Participants

The only inclusion criteria for ATTENTIVE was that each participant had to be a practicing GP; this was established from the first question in the survey. Non-practicing GPs were excluded. GPs were invited by email without offering an incentive. For this study, only GPs that provided an answer for all eight case vignettes were included; this stipulation enabled us to calculate GP treatment probability over all the cases.

Survey

In short, the survey contained eight case vignettes of oldest-old patients (aged >80 years; males and females) that consulted their GPs for a routine visit without showing blood pressure-related symptoms or receiving antihypertensive treatment. All case vignettes differed in three primary characteristics: systolic blood pressure (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. We piloted and then translated the questionnaire into 21 languages (Additional file 1 in [10]). SurveyMonkey (www.surveymonkey.com, Palo Alto, CA, USA) was used to build the online questionnaire. As an exception, in Ukraine (where web access was limited) a paper questionnaire was used.

Variables

The outcome of this study was the proportion of case vignettes for which GPs decided to start antihypertensive treatment, i.e. GP treatment probability. GPs were dichotomised into two groups according to the median of GP treatment probability, i.e. ≤50% 'low', >50% 'high'.

The exposure was CVD burden per country. CVD burden per country was defined as: the ratio of DALYs in persons aged >70 years lost due to ischemic heart disease and/or stroke and the total DALYs lost in persons aged >70 years. These data were retrieved from the GBD database (hosted by the Institute for Health Metrics and Evaluation). Data specific for individuals >80 years were not available why we chose the next best estimate (>70). The GBD is a public

database capturing national estimates on total and disease-specific DALYs [12]. The country-specific CVD burden ranged from 16% in France to 59% in Ukraine (Appendix figure 1). The countries were divided into two groups according to the median of CVD burden, i.e. <22.5% ('low') and ≥22.5% ('high').

Country-specific life expectancy at age 60 years was considered a possible effect modifier, and the prevalence of persons aged ≥80 years per country was considered a possible confounder for the association between CVD burden and GP treatment probability. Life expectancy at age 60 years was obtained from the 2015 Global Health Observatory data repository of the World Health Organisation [13]. Prevalence of oldest-old was available from the 2015 report of the United Nations [14]. Data specific for individuals >80 years were not available why we chose the next best estimate (>60). Both covariates were dichotomized in two quantiles according to their medians: life expectancy at age 60 years low (<24 years) and high (≥24 years) and prevalence of oldest-old low (<4.6%) and high (≥4.6%).

Per GP, we included gender and years of experience on an individual level from the ATTEN-TIVE data. Years of experience was categorized into two groups of about equal sizes: <15 years ('low') and ≥15 years ('high').

The previous ATTENTIVE study [10] showed that patient characteristics (SBP, CVD and frailty) were independently associated with the GPs' decisions to start antihypertensive treatment. However, for the present study, we were only interested in the overall effect of CVD burden on GP treatment probability; therefore, as an outcome, we chose the proportion of all case vignettes for which GPs decided to start treatment, and neglected the case characteristics (SBP, CVD and frailty).

Statistical analysis

The ATTENTIVE dataset was visually explored and checked for missing data, outliers and inconsistencies. New dichotomized variables were generated (after visual checks) by grouping of the distributions using histograms. The exposure and all covariates were checked for multicollinearity by calculating pairwise correlation coefficients.

Chi-squared tests and unadjusted odds ratios (OR), as well as 95% confidence intervals (CI), were used to investigate whether the exposure (CVD burden) and the other independent variables (GP gender/years of experience, life expectancy at age 60, and prevalence of oldest-old) were associated with the outcome (GP treatment probability).

On a country level, continuous data of CVD burden and averaged GP treatment probability per country were visualized using scatter plots. A linear regression line with 95% CI was

derived using a univariate linear regression model. In a sensitivity analysis, this analysis was restricted to those countries where >60% of the GPs responded to the survey.

Chi-squared tests were then used to investigate whether CVD burden was associated with any of the independent variables and, if not on a causal pathway, these were considered to be potential confounders.

All potential confounders were tested for the degree of confounding and/or effect modification using the Mantel-Haenszel test of homogeneity of ORs (detailed in Appendix table 1). As pre-specified, the causal model presented stratum-specific ORs and 95% CI for low and high life expectancy at age 60 years. Variables that confounded the association between the exposure and the outcome were included in the final model.

A two-sided p-value of 0.05 was considered statistically significant. All analyses were performed in STATA release 14.2 (Stata Corp, College Station, TX, USA).

RESULTS

In the ATTENTIVE study, 2,543 GPs from 29 countries participated. The median response rate for all countries was 26% (21 countries with <60%, 8 countries with ≥60%). Of those participating, 1,947 GPs (76.6%), provided an answer for all eight case vignettes.

Table 1 presents the baseline characteristics of the participating GPs and the countries, stratified by GP treatment probability. There were 1,160 (59.6%) GPs with a low and 787 (40.4%) GPs with a high GP treatment probability. Countries with a high CVD burden showed a positive association with GP treatment probability (OR 3.70, 95% CI 3.03, 4.52; p<0.001).

Figure 1 shows the association between CVD burden and GP treatment probability on a country level using continuous data. Strong evidence was found for an association between CVD burden and GP treatment probability (p<0.001). Of all countries, the Netherlands had the lowest GP treatment probability (34%) and one of the lowest CVD burdens (16%), whereas Ukraine was among the countries with both the highest GP treatment probability (88%) and CVD burden (59%). When restricting the analysis to countries with a response rate of >60%, the sensitivity analysis confirmed this association (p=0.001) (Appendix figure 2).

In countries with a high CVD burden, the ORs for treatment was higher compared to countries with a low CVD burden (3.70, 95% CI 3.00, 4.57). Country-specific prevalence of oldest-old was a significant confounder (adjusted OR 2.71, 95% CI 2.17, 3.38) while GP gender and

Table 1. Baseline characteristics of general practitioners (GPs) and countries, and their association with high GP treatment probability to start antihypertensive treatment in oldest-old (n=1,947).

Characteristics	GP treatment probability		Crude odds ratio of high GP treatment probability (95% CI)	P-value
	Low (≤50%) (n=1,160)	High (>50%) (n=787)		
GP Gender				
Female	535 (54.6)	445 (45.4)	1.00 (reference)	
Male	625 (64.6)	342 (35.4)	0.66 (0.55, 0.79)	<0.001
Experience as GP				
<15 years	558 (56.7)	427 (43.4)	1.00 (reference)	
>15 years	602 (62.7)	358 (37.3)	0.78 (0.65, 0.93)	0.007
Prevalence of oldest-old				
Low	404 (45.0)	493 (55.0)	1.00 (reference)	
High	756 (72.0)	294 (28.0)	0.32 (0.26, 0.38)	<0.001
Life expectancy at age 60 years				
Low	216 (36.4)	378 (63.6)	1.00 (reference)	
High	944 (69.8)	409 (30.2)	0.25 (0.20, 0.30)	<0.001
Cardiovascular disease burden				
Low	930 (69.4)	411 (30.7)	1.00 (reference)	
High	230 (38.0)	376 (62.1)	3.70 (3.03, 4.52)	<0.001

P-values are from univariate logistic regression

Association of country-specific cardiovascular disease burden on mean GP treatment probability per country in oldest old

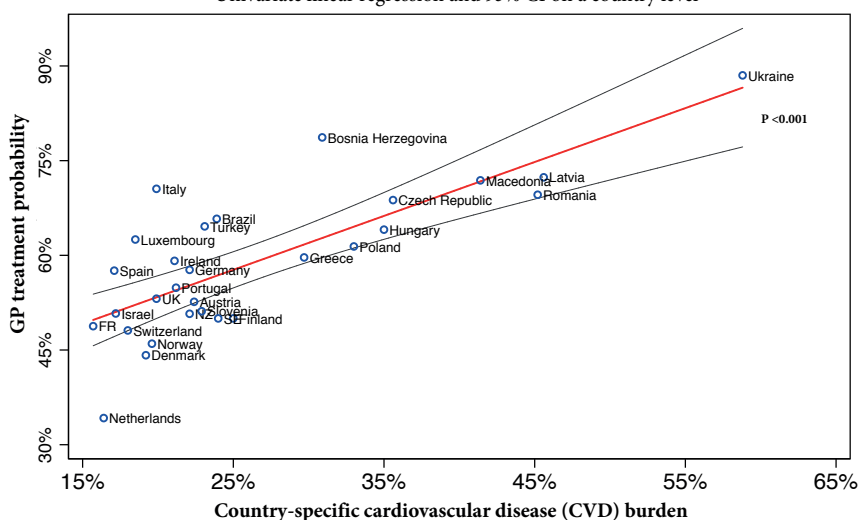Univariate linear regression and 95% CI on a country level

Figure 1. Association between country-specific cardiovascular disease burden and mean general practitioner (GP) treatment probability per country in oldest-old. Univariate linear regression was used (bold line), 95% confidence intervals (fine lines) and p-value. FR=France; NZ=New Zealand; SE=Sweden, UK=United Kingdom

GP years of experience were not confounders. Life-expectancy at age 60 years was an effect modifier (Mantel-Haenszel test of homogeneity p=0.005) of the association between CVD burden and GP treatment probability. Therefore, we included country-specific prevalence of oldest-old in the multivariate model and present stratum specific estimates for low and high life expectancy at age 60 years.

In the final model (Table 2), GPs working in countries with a high CVD burden and a low life expectancy at age 60 years were more likely to start antihypertensive treatment in the oldest-old (adjusted OR 2.18, 95% CI 1.12, 4.25) compared to their counterparts in countries with a low CVD burden. In countries with a high life expectancy at age 60 years, there was no evidence for such an association (adjusted OR 1.06, 95% CI 0.56, 1.98).

Table 2. Final model including 1,947 GPs for the association of cardiovascular disease (CVD) burden on GP treatment probability in oldest-old.

	Fully-adjusted odds ratio of GP treatment probability (95% CI)
CVD burden (stratum-specific)	
Low life expectancy at age 60	2.18 (1.12, 4.25)
High life expectancy at age 60	1.06 (0.56, 1.98)
Prevalence of oldest-old	0.48 (0.39, 0.59)

DISCUSSION

The clinical dilemma when deciding whether (or not) to start antihypertensive treatment in the oldest-old may not only be explained by differences in patient characteristics but also in country-specific characteristics. In the present study including 1,947 GPs from 29 countries, a high country-specific CVD burden was associated with a higher probability of GPs deciding to start antihypertensive treatment in patients aged >80 years. However, the association was modified by country-specific life expectancy at age 60 years. While there was a positive association for GPs in countries with a low life expectancy at age 60 years, there was no association for GPs in countries with a high life expectancy at age 60 years. These findings (partly) explain some of the large variation seen in the decision as to whether or not to treat hypertension in the oldest-old [10].

Strengths and limitations

The inclusion of a large number of GPs from a large number of countries (in Europe and beyond) is a strength of this study; this allowed us to study the relation between country-specific health characteristics and GP decisions in an ecological analysis. Also, we could describe GP treatment probabilities in countries that are not usually included in international studies.

This study also has limitations. First, GP treatment probability was self-reported and based on fictive cases stories and not on, for example, chart reviews. Second, the overall response rate was only 26% across all countries, which is not uncommon in surveys involving GPs [15]. However, our response rate was not lower than in other GP survey studies [16, 17] and low response rates of GPs do not necessarily result in selection bias [18, 19]. In addition, when restricting our analysis to countries where the GPs responded for ≥60%, the results remained unchanged. Third, we can only report associations and not causation as this was an observational study with limitations such as residual confounding. However, we explored and reported patient-related factors associated with GP treatment probability in an earlier study [10].

Findings in relation to other studies

The results from this study suggest that GPs in countries where their 60-year-old patients will die (on average) before the age of 84 years, base their decision to start antihypertensive treatment in the oldest-old not only on the individual risk or prevalence of oldest-old, but also on the CVD burden of their country. In our opinion, the daily experience and case load provides GPs with sufficient knowledge to assess CVD burden and country-specific DALY of the patients that they see and treat, even without knowing the exact burden. DALYs due to CVD burden are not only a problem in high-income countries but mostly in low- and middle-income countries (LMIC) [20]. The inequity in cardiovascular health in LMIC compared to high-income countries, calls for empowering GPs with the knowledge/skills to meet the requirements in these countries [21]. While our study shows that, in countries with a lower life-expectancy, GPs are more inclined to treat hypertension when CVD burden is high, the effects of such treatment on e.g. mortality or patient-relevant outcomes such as quality of life, remain unclear. Treatment goals for hypertension (especially in older patients) are constantly changing [22]. Although trials including oldest-old show a clear benefit of lowering blood pressure [23, 24], the generalizability of these studies is still debated [22, 25-27]. In this clinical dilemma, prognosis and life expectancy are issues that GPs relate to in the decision-making process in older patients [6].

Meaning of the study

Future high-quality observational studies, or new trials including the otherwise excluded frail patients with multimorbidity, should be conducted to provide more evidence for decision-making with respect to hypertension treatment in the oldest-old. With evidence that can be generalized for GP patients that are frail and multimorbid, the implementation into daily practice should be thoughtfully planned. Our study found also a crude association of female GPs and GPs with a shorter than 15-year experience to treat more often hypertension in oldest-old. Future studies could further investigate if this association is real. These steps are

needed to overcome inequities in treatment decisions across countries with different CVD burdens and life expectancies.

Conclusions

The clinical dilemma when deciding whether (or not) to start antihypertensive treatment in the oldest-old appears not only to be explained by differences in patient characteristics but also in country-specific health characteristics. In this ecological comparative study, GPs living in countries with a high CVD burden and low life expectancy at age 60 years were more likely to start antihypertensive treatment in the oldest-old than GPs in countries with a low CVD burden and a high life expectancy at age 60 years.

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CVD burden, life-expectancy at age 60, and prevalence of oldest-old per country
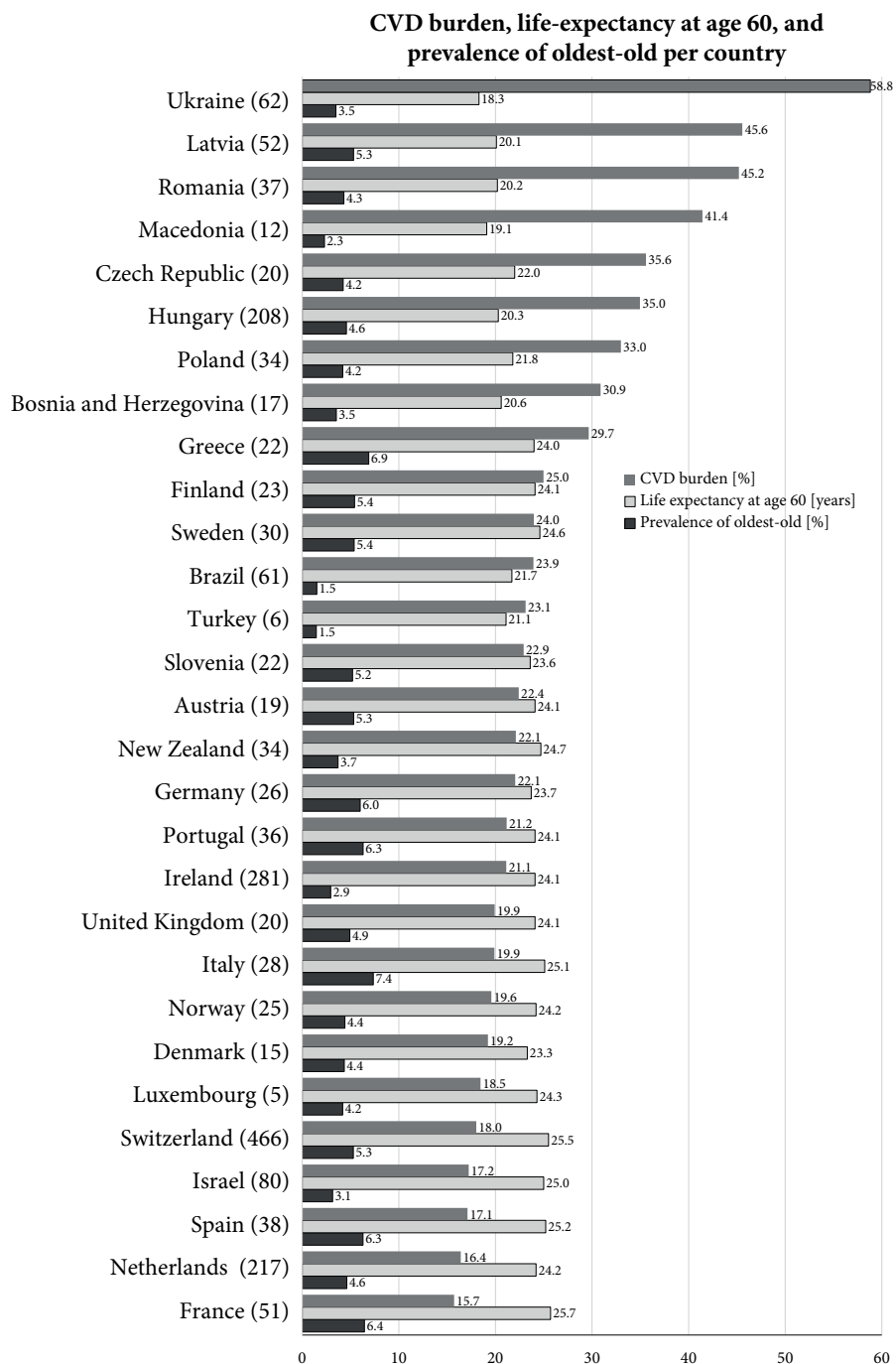
Appendix figure 1. Characteristics of all 29 included countries (number of GPs per country)

Association of country-specific cardiovascular disease burden on mean GP treatment probability per country in oldest old

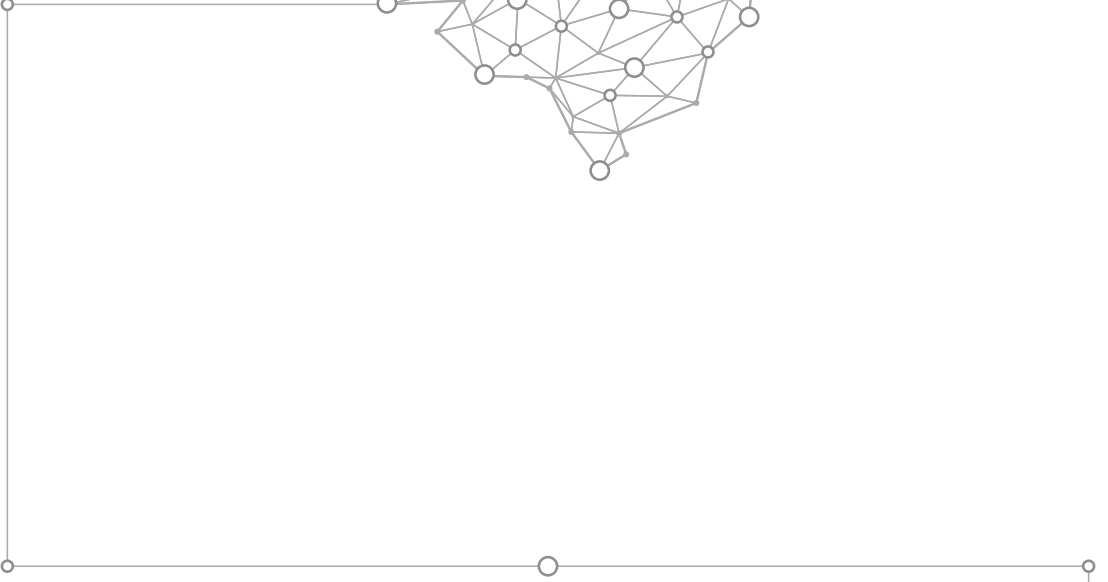Univariate linear regression and 95% CI on a country level
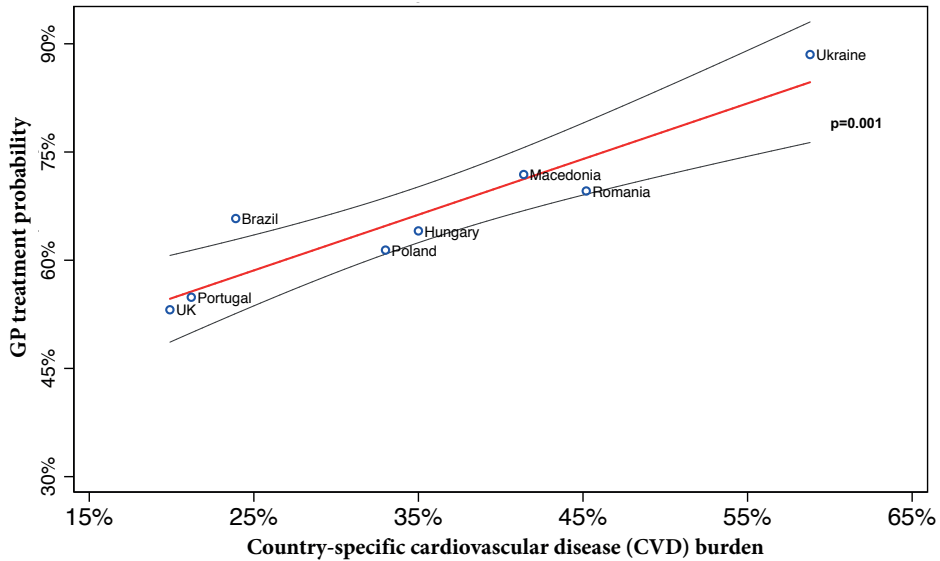
Appendix figure 2. Sensitivity analysis including only countries with a response rate of >60% (n=8). Association between country-specific cardiovascular disease (CVD) burden on mean general practitioner (GP) treatment probability per country in oldest-old. Univariate linear regression was used (bold line), 95% confidence intervals (fine lines) and p-value. UK=United Kingdom

Appendix table 1. Assessing confounding and testing for effect modification on the association of cardiovascular disease (CVD) burden on GP treatment probability in oldest-old.

	Odds ratio of GP treatment probability (95% CI)	P-value
Unadjusted effect of CVD burden	3.70 (3.00, 4.57)	
Effect of CVD burden adjusted for …		
Gender	3.55 (2.87, 4.41)	0.19
Female	4.01 (3.01, 5.34)	
Male	3.01 (2.18, 4.16)	
High experience (15 years)	3.73 (3.02, 4.60)	0.87
Low	3.79 (2.81, 5.12)	
High	3.66 (2.71, 4.93)	
Life expectancy at age 60	1.48 (0.97, 2.29)	0.005
Low	2.96 (1.53, 5.72)	
High	0.82 (0.44, 1.53)	
Prevalence of oldest old	2.71 (2.17, 3.38)	0.57
Low	2.59 (1.96, 3.41)	
High	2.96 (2.06, 4.24)	

P-values are from Mantel-Haenszel test of homogeneity of odds ratios. Variables highlighted in grey were chosen for the final model.

7

General Discussion

Physicians face a clinical dilemma when they treat hypertension in >75-year-olds, since this population varies widely in cognitive and physical function. Some are very healthy, while others have several chronic diseases (multimorbidity), take many different drugs (polypharmacy), or are frail. This thesis began with the case of a frail 90-year-old patient with polypharmacy (Mrs S) and her question about her ideal blood pressure target under antihypertensive treatment, given her age, medical conditions, and living situation. GPs aim to reduce the risk that Mrs S will suffer from a severe stroke or myocardial infarction, and also to preserve her function. As Mrs S put it, "I don't want to live longer, but I want to be independent for as long as possible".

In the context of Mrs S, this thesis set out to 1) measure the prevalence of polypharmacy in older patients; 2) 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 cardio-vascular disease burden and life expectancy. Below, the main findings and limitations are discussed, and suggestions are made about clinical practice, and directions for future research.

MAIN FINDINGS OF THE THREE AIMS

Hypertension has the strongest association with polypharmacy

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 about prevalence and drivers of polypharmacy.

Chapter 2 established the high prevalence of polypharmacy in patients from four university primary care settings in Switzerland. In the whole age group (50-80 years), about 40% had polypharmacy, but among 75-80-year-olds, more than 50%, and some took even 10 or more long-term medication. Patients with hypertension in the oldest age group had about a 9-fold greater risk of polypharmacy.

Mrs S' hypertension is a factor in her polypharmacy, since, like many her age, she might need to take more than one drug to reach the blood pressure target set by current guidelines. In a sample of >60-year-old diabetic patients from the UK, about every third patient needed at least three different drugs to reach their blood pressure target of <150/85mmHg [1]. Hypertension, diabetes mellitus, and chronic kidney disease are all strongly related to CVD, so patients with these comorbidities are often prescribed more drugs than recommended for

both primary and secondary prevention (e.g. aspirin, statins) [2-5]. The association we found between CVD and polypharmacy aligns with the results of other studies [6, 7], as does the association between polypharmacy and potentially inappropriate prescriptions [8].

Our study underlined the importance of reconsidering each prescription. Age and number of chronic conditions are key factors, as is type of disease (e.g. hypertension). The STOPP/START criteria may be useful here [9, 10]. Because applying the whole set of explicit criteria is time-consuming and hard to implement in everyday clinical practice, physicians would appreciate another solution. Software programs that address polypharmacy are being developed and tested for effectiveness [11]. GPs could make a sound clinical judgment and then take shared decision-making approach to determine which prescriptions they should start, continue or deprescribe. This approach is even more sensible to take with older patients with frailty.

Low SBP associated with increased mortality and cognitive decline in patients with frailty

Deciding on the optimal SBP in older patients with frailty is not a simple task. GPs face a dilemma for GPs because results cannot be generalised from hypertension trials that excluded older and frail patients.

In **Chapters 3 and 4,** we thus tested for an association between low SBP and mortality, cognitive function, daily functioning, and QoL in >75-year-olds under antihypertensive treatment. We stratified our analyses on frailty (defined as low hand grip strength or complex health problems) to test our hypothesis in patients who are usually excluded from previous trials.

In **Chapter 3**, we analysed the Leiden 85-plus Study, a Dutch population-based cohort (n=599) of all 85-year-olds, followed up for five years. We found low SBP under antihypertensive treatment was associated with increased all-cause mortality and accelerated annual cognitive decline. But frailty indicated by low hand grip strength modified the association with cognitive function: frail patients suffered accelerated cognitive decline. In non-frail participants and in those not treated for hypertension, SBP and mortality/cognitive function were not related.

In ISCOPE, a more recent cohort (n=1,266) with younger participants (all ≥75 years-old) and a one-year follow-up (described in **Chapter 4)**, we confirmed low SBP was similarly associated with cognitive decline with no negative effect on daily functioning and QoL in participants under antihypertensive treatment. Again, the association was modified by the presence of frailty (defined as having complex health problems): in participants with complex health problems, low SBP and cognitive decline were associated. In line with findings from the

Leiden 85-plus Study, we found no negative association of low SBP and cognitive decline in those not under antihypertensive treatment.

In the context of Mrs S, the Leiden 85-plus Study offers new insights because it was population-based, and thus generalizable to the general population. The study also had a sufficiently long follow-up of 5 years. The ISCOPE study confirmed our results in a slightly younger population of older patients that were followed-up about 10 years after the Leiden-85 plus Study ended, so we conclude that these findings are very likely to be true regardless of the sample or time period being investigated.

Our findings on accelerated cognitive decline are in line with other cohort studies [12, 13]. However, the only other study that analyzed patients under antihypertensive treatment separately from those without treatment was the landmark study by Mosello *et al.* [14]. Mosello's cohort differs in setting (outpatient memory clinics), follow-up time (<1 year) and population and included only patients with dementia or mild cognitive impairment, while we included participants with the full range of cognitive function at baseline. Our study had a larger sample and was the first to show these associations between low SBP and cognitive decline in the general population, over an observation period of one or more years.

Other studies of patients aged >60 found no association when adjusting for antihypertensive treatment [15], or found an association between higher SBP and better cognitive function and lower risk of dementia [16]. Our studies added to the evidence that age modifies the association [17]. In studies that included >60-year-olds there was no association between SBP and cognitive decline [15], and no association between higher SBP and lower risk of dementia [16]. But in >75-year-olds, low SBP predicted the onset of dementia [18] and was associated with worse cognitive function [19]. The association reverses at about age 75, when hypertension no longer predicts dementia [18] and is not associated with worse cognitive function [19]. There is evidence that existing vascular injury cannot be reversed in late life, and low SBP in late life could disturb the hemodynamic regulation of the heart and brain and reduce cognitive function [20, 21].

We found no evidence SBP was associated with daily functioning, though prior studies identified both positive and negative associations [19, 22, 23]. A cohort study of 35 centenarians in Poland found higher SBP had a beneficial effect on daily activity [19]. The Leiden 85-plus Study found higher SBP levels were associated with lower ADL disability over 5 years [22]. But a US longitudinal cohort study of about 600 75-year-olds found high SBP was associated with declining physical function (measured by gait speed) over 10 years of follow-up [23].

Most studies that assessed the association of SBP with function in old age did not assess QoL. We know of only a Polish cohort of 11,500 patients, which found that those under antihypertensive treatment had optimal QoL with higher SBP [24].

Despite limited evidence, physicians must decide every day on appropriate treatment for hypertension in older patients with frailty like Mrs S [25, 26]. Physicians want to reduce stroke and myocardial infarction risk and preserve cognitive function, daily functioning and QoL. Benetos *et al.* [27] suggest GPs to take an individualized approach when treating hypertension in older patients with frailty. Since we showed that higher blood pressure under treatment is better for cognitive function, there is an argument for increasing blood pressure by deprescribing antihypertensive treatment. Early trials, like the Dutch DANTE study, asked if deprescribing antihypertensive medication improved cognitive function in older patients with mild cognitive impairment, but found no evidence of this effect after 16 weeks of follow-up [28]. Long term effects of deprescribing antihypertensives are still uncertain, but a recent Cochrane review found withdrawing from antihypertensive therapy in old age did not increase mortality [29]. We encourage 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

We speculated that GPs practicing in countries with a high CVD burden from stroke and myocardial infarction might decide to treat Mrs S differently than GPs in countries with low burden of CVD. We thus set out to collaborate with GPs from 29 countries in Europe, Brazil, Israel, and New Zealand. Using case-vignettes, similar to the story of Mrs S, revealed that the 2,543 GP participants made very different decisions about when and if to start antihypertensive treatment. To try to explain part of the variation, we also categorized countries in groups of CVD burden based on disability adjusted life years (DALY) [30] and life expectancy at age 60 [31].

In **Chapter 5**, we found wide variation in how GPs decided to start antihypertensive treatment in old age. Dutch GPs advised starting antihypertensive treatment in 34% of all case-vignettes, while GPs from Ukraine did so in 88%. As hypothesized, frailty was important for GPs when they decided about antihypertensive treatment. In **Chapter 6**, we confirmed that in countries with a high CVD burden, GPs were more likely to advise starting antihypertensive treatment. This association was modified by country-specific life expectancy at age 60. While there was a positive association for GPs in countries with low life expectancy at age 60 years, this association was absent for GPs in countries with high life expectancy.

The wide spectrum of recommendations and lack of clear evidence may explain some of the variation between GPs in different countries. Differences may also be caused by national guidelines/campaigns. This study did confirm our hypothesis that GPs factor in frailty when they treat hypertension in patients like Mrs S. GPs were also less likely to treat frail patients, even after we adjusted for SBP and history of CVD. Our results are in line with findings from a Dutch qualitative study where vulnerability was a significant patient-related barrier for GPs, who hesitated to implement guidelines for secondary cardiovascular prevention in old age [32]. The only other published study on this topic, Mermans *et al.,* surveyed GPs in Belgium and also found wide variations in GPs' intentions to treat hypertension in old age, but frailty was not associated with variation found in Belgium [33]. On an international level, when we included many countries and more GPs, we found frailty was an important factor influencing GPs' treatment decisions.

Part of the international variation could be explained by national differences of CVD burden and life expectancy at age 60. We believe GPs base their assessment of CVD burden and country-specific DALY on their own experience and case load, even if they do not know the exact numbers. This might explain why Mrs S, who lives in Switzerland where the CVD burden is low, and life-expectancy is high, is likely to have a GP who is more concerned about prescribing antihypertensive treatment. DALYs caused by CVD burden pose a problem in high-income countries, but the problem is greater in low- and middle-income countries [34]. To address this inequity in cardiovascular health between low-, middle- and high-income countries remains challenging [35].

These studies confirmed the hypothesis that GPs do not treat hypertension in old age uniformly, and that patient characteristics, national burden of CVD, and life expectancy play a role in their decisions, as in the case of Mrs S. There is a need for more high-quality cohort studies and, ideally, new hypertension trials that deliberately include >75-year-olds with frailty. Future studies should seek to determine if treatment variation can be explained by, e.g., the fact that individual GPs follow different guideline recommendations. Qualitative studies could help us better understand the variation we identified.

METHODOLOGICAL CONSIDERATIONS

Study design and data from the studies presented in this thesis have some methodological limitations, including selection bias, the question of causality in associations, the possibility of reverse causality, confounding, missing data, and risk of misclassification.

Selection Bias

Selection bias can occur when individuals included in a study differ from individuals not included or those that did not participate: an association between exposure and outcome could differ between those included and those not. Low response rates usually raise concerns about selection bias.

For example, in **Chapter 2**, we restricted our analyses to patients aged 50 to 80, so we cannot draw conclusions about younger or older patients. Ideally, our sample would have included patients over 80, but the CORIF dataset was extracted from medical charts and we could not revisit these charts to collect data from those >80-year-olds. Prevalence of polypharmacy increased linearly with age, but it might have increased even more steeply in >80-year-olds.

In **Chapter 4**, about 63% of invited individuals responded to the baseline questionnaire in ISCOPE. Non-responders were more frail but otherwise similar to responders, though selection bias cannot be ruled out.

In **Chapters 5 and 6**, our overall response rate was only 26% across all countries, which is not uncommon in surveys of GPs [36]; this response rate was not lower than in other surveys [37, 38]. Low response rates of GPs do not necessarily create selection bias [39], since also studies 'with low response rates may provide a representative sample' [40]. For example, when we restricted our analysis in Chapter 6 to countries where ≥60% of GPs responded, our results were robust.

Association versus causation

When chance, bias, or confounding are unlikely to explain a given association, we can assume the association is true. The next step to judging causality can only be taken based on current available evidence. The GRADE framework [40] situates such associations in this context. Bradford Hill's criteria for causation can be applied [41] to determine if associations can be considered to be causal. For example, several factors suggest a causal association in **Chapters 3 and 4**, but do not prove causality in the relationship between low SBP, and mortality and cognitive function in >75-year-olds. Using Bradford Hill's criteria, we determined the following: 1) SBP, antihypertensive treatment and cognitive function were strongly associated in this study, consistent with other studies. 2) This study established a temporal relationship between SBP values measured a year prior to study inclusion and assessments of outcome one year after (**Chapter 4**), and up to five years after (**Chapter 3**). 3) We also identified a pattern of dose-response relationship because SBP had an incremental effect on mortality and cognitive function in old age. 4) There is more evidence for the biological plausibility of an association between SBP, antihypertensive treatment and cognitive function. Existing vascular injury

cannot be reversed in late life; where it is present, antihypertensive treatment may disturb the hemodynamic regulation of the heart and brain and reduce cognitive function [20, 21].

Confounding

When an exposure is associated with an outcome, there could be other factors (confounders) that are all or in part responsible for the association. For example, age, sex, or many others. Confounding can be controlled for in the study design by randomization, restriction, matching, stratification, or adjusting in a multivariable model. For example, in **Chapters 3 and 4**, where we adjusted for a set of predefined known confounders such as age, sex, and history of CVD. However, other potentially important confounders were unavailable. For example, there could be other reasons that we do not know for why GPs prescribe or do not prescribe antihypertensive treatment in old age, which is a problem of confounding by indication. This might have led to residual confounding. But in the Netherlands, GPs issue national guidelines (NHG Standaard) that also make evidence-based recommendations on antihypertensive therapy in old age [42]. We know from international comparisons that almost all Dutch GPs use the NHG Standaard when they treat hypertension in old age (unpublished subgroup analysis of the ATTENTIVE Study in Chapter 5 and 6). ATTENTIVE helped us to identify a set of confounders most often mentioned by GPs when they decide on antihypertensive treatment and define SBP goals in old age.

Reverse causality

Reverse causality means that factor X and Y are associated differently than one would expect. While common sense often allows us to exclude reverse causality (e.g., lung cancer does not cause smoking), in other examples exclusion can be less trivial. For example, in **Chapters 3 and 4**, our observations of the relationship between SBP and cognitive function can also be explained by reverse causality, if cognitive decline leads to lower SBP. To minimize the risk of bias, in **Chapter 3**, patients who died within 12 months of follow-up were excluded from the analysis to reduce the risk of reverse causality. In **Chapter 4**, we used the SBP measure taken a year before baseline, and the cognitive function measure taken after one year.

Missing data and risk of misclassifications

Missing data is a common problem in clinical research when some of the participants are not measured or participants did not answer all questions in a questionnaire. Missing data leads to a biased dataset restricted only to participants with complete data. There are two types of missing data. If some data is missing completely at random (e.g. postal questionnaires not returned to the study centre because they are lost), the associations found in the remaining data are likely not affected by missing data. But when data is not missing at random (e.g. frail patients cannot perform a test) the identified associations are biased. For example, in **Chapter 4**, about 15% of participants had no SBP measurement in the year before they were

included in the study. GPs may have been less likely to measure or record SBP in participants at lower cardiovascular risk, or to measure at intervals greater than one year. In **Chapter 3**, a research nurses had not taken SBP measurements at baseline for about 5% of participants in this cohort study. Since the association between SBP and cognitive function was the same in a sensitivity analysis that included only participants with low cardiovascular risk (no history of CVD), we do not think that excluding participants with missing SBP data changed the associations. In **Chapter 3 and 4**, we classed antihypertensive therapy (yes or no) based on prescriptions recorded in EMRs. If participants were prescribed antihypertensive drugs, but did not adhere to the treatment regimen, they would have been misclassified as exposed to therapy. However, patients treated for hypertension in the Netherlands adhered better than patients in seven other European countries [43], so the risk of misclassification was lowest in this country where both studies were conducted.

CONCLUDING REMARKS

Earlier, we met Mrs S, a 90-year old woman under treatment for hypertension, consulting her GP for a routine check of her blood pressure, which was 154 mmHg in the office and between 145-150 mmHg at home. She, and patients like her, are unlikely to be included in randomized trials that contribute evidence for the development of clinical guidelines on how to treat hypertension in old age.

From a clinical perspective, the evidence presented in this thesis and other current evidence suggest we consider moving cautiously to re-define SBP treatment goals, especially in older patients with frailty [27]. Mrs S' GP could decide that her current SBP of 154 mmHg is acceptable and it might be harmful to reduce it to <130 mmHg. Her GP might want to explain his dilemma to her: The results of existing trials are valid but cannot be generalized to her situation. Even though observational studies show the same associations in participants like Mrs S, we cannot prove causality. But we do not believe that trials and observational studies conflict. Together, both support the goal of individualizing antihypertensive treatment in older patients with frailty. This approach might also help us to reduce the wide treatment variation we identified across 29 mainly European countries, although these variations are explained not only by patient characteristics but also by disease burden and life expectancy in each country.

We should conduct new trials to test the effectiveness and safety of deprescribing antihypertensive medications and raising SBP. The most recent Cochrane review of the effects of deprescribing was uncertain about its effect [29], but mortality did not significantly increase in participants allocated to deprescribing from antihypertensive treatment. The next round
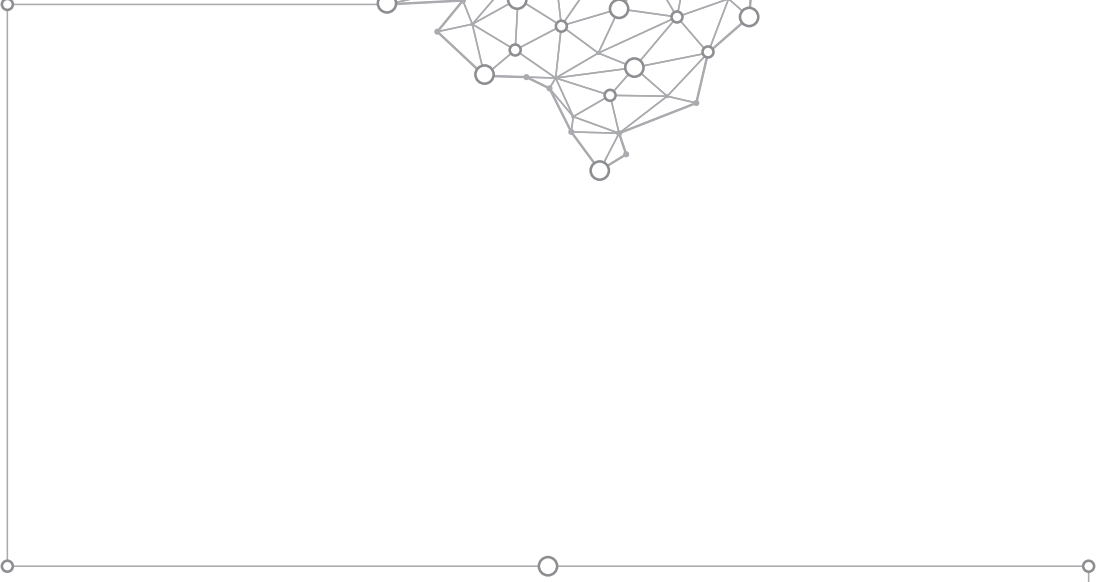
of trials should test the long-term effectiveness and safety of deprescribing antihypertensive therapy to raise SBP in >75-year-olds with frailty.

Patients such as Mrs S often have polypharmacy, and conditions like hypertension combined with age to increase risk of polypharmacy. Mrs S is >75-years-old with frailty. In patients like her, we found an association between low systolic blood pressure and risk of mortality and cognitive decline, with no negative effect on daily functioning or quality of life. We did not find these associations in participants without antihypertensive treatment or frailty. Finally, we found wide variation in the advice given by GPs across Europe, Brazil, Israel and New Zealand on starting antihypertensive treatment in Mrs S' case. Frailty and burden from cardiovascular diseases explained part of the variation. This study lays the groundwork for individualized treatment goals in >75-year-olds with hypertension, and for new deprescribing trials to test the effectiveness of stopping/reducing antihypertensive treatment in >75-year-olds with frailty. Patients like Mrs S will benefit from the findings of such studies, and GPs might face less of a clinical dilemma when they treat hypertension in old age.

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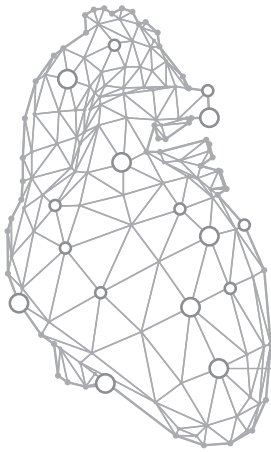
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Summary

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.

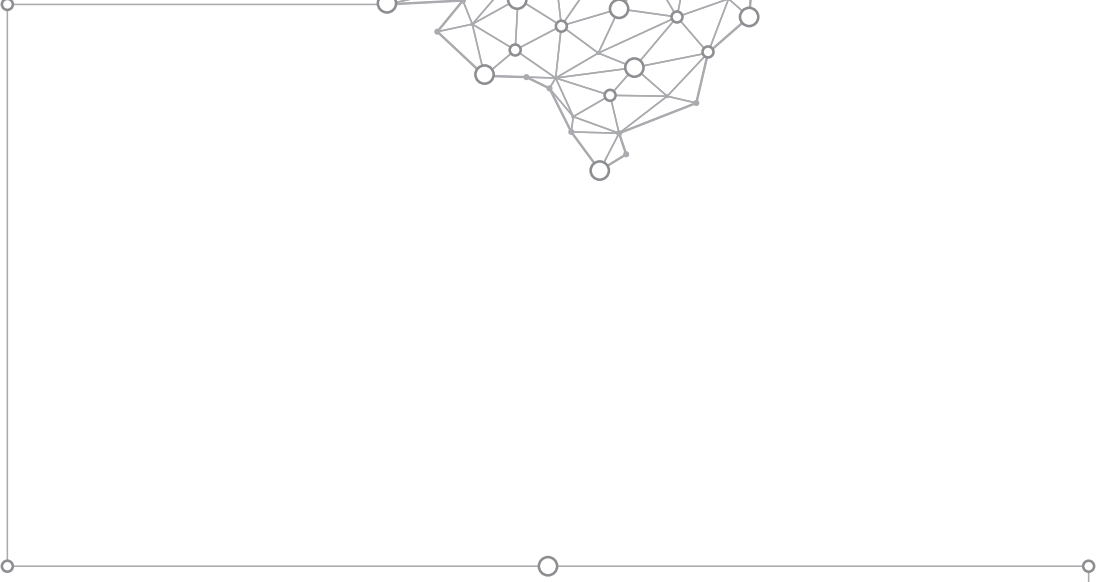**Variation in antihypertensive treatment in old age, according to GPs**

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.
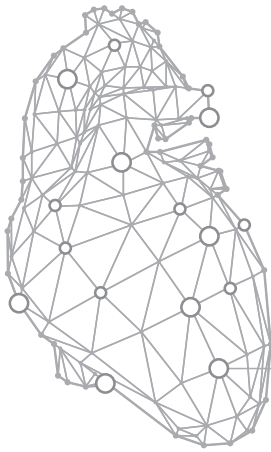
9

Other chapters
Nederlandse samenvatting
Deutsche Zusammenfassung
Bibliography
Acknowledgements

NEDERLANDSE SAMENVATTING

Artsen staan voor een klinisch dilemma wanneer zij de streefwaarde moeten vaststellen van een optimale systolische bloeddruk (SBD) voor ouderen, en in het bijzonder bij ouderen vanaf 75 jaar. Deze populatie van 75-plussers kenmerkt zich door een sterke variatie in cognitief en fysiek functioneren. Sommigen zijn zeer gezond, anderen hebben meerdere naast elkaar bestaande chronische aandoeningen (multimorbiditeit) en worden daarom behandeld met meerdere medicijnen (polyfarmacie) of zijn kwetsbaar.

Met het oplopen van de leeftijd stijgt de bloeddruk als gevolg van arteriële stijfheid. Er bestaat discussie of het gunstig is om hypertensie op oudere leeftijd te behandelen, vooral bij 75-plussers met multimorbiditeit, polyfarmacie of kwetsbaarheid. In grote trials naar de effecten van behandeling van hypertensie is aangetoond dat het verlagen van de SBD bij 60-plussers gunstig is en dat dit het risico op myocardinfarcten, beroerten en sterfte verlaagt. Dit geldt zelfs voor de subgroep van 80-plussers in deze grote trials. Echter, het ontbreekt in deze trials aan generaliseerbaarheid; oudere patiënten met multimorbiditeit en kwetsbaarheid zijn meestal uitgesloten.

Tegelijkertijd zijn er vanuit observationele studies zorgen ontstaan over het teveel verlagen van de SBD. Zo zijn er in meerdere cohort studies associaties gevonden tussen een lage SBD, een toename in sterfte en versnelde cognitieve achteruitgang, vooral bij 75-plussers. Het advies in de huidige internationale hypertensierichtlijnen om bij alle patiënten van 60 jaar en ouder de SBD te verlagen, zelfs tot waarden lager dan 130mmHg, voedt de discussie over de voor- en nadelen van het te veel verlagen van de SBD in 75-plussers nog meer.

In **Hoofdstuk 1** is dit dilemma samengevat in een vignet van mevr. S, een kwetsbare 90-plusser met multimorbiditeit en polyfarmacie die bij de huisarts kwam voor een routinecontrole van haar bloeddruk. Haar SBD was 154 mmHg bij het gebruik van antihypertensiva. Middels deze behandeling tracht de huisarts mevr. S. te beschermen tegen een beroerte en een myocardinfarct. Tegelijkertijd tracht hij haar cognitief en dagelijks functioneren en kwaliteit van leven te behouden. Mevr. S. vertegenwoordigt een groep mensen die vaak wordt uitgesloten van deelname aan hypertensie trials. Hierdoor kan niet met zekerheid gesteld worden dat de resultaten van deze trials ook van toepassing zijn op mevr. S.

Het doel van dit proefschrift is het vergroten van het wetenschappelijk inzicht over de effecten van de behandeling van hypertensie bij 75-plussers. De drie doelen van dit proefschrift zijn: 1) het meten van de prevalentie van polyfarmacie in oudere patiënten; 2) het testen van de associatie tussen lage SBD, sterfte, cognitief functioneren, dagelijks functioneren en kwaliteit van leven bij oudere patiënten die behandeld worden met antihypertensiva; en 3) het verkrij-

gen van inzicht in de variatie in behandeling van hypertensie bij ouderen door huisartsen uit verschillende landen en wat de invloed van kwetsbaarheid, cardiovasculaire ziektelast en levensverwachting hierop is.

Polyfarmacie in relatie tot cardiovasculaire preventieve medicatie

De meeste behandelrichtlijnen voor chronische ziektes zijn gericht op slechts één aandoening. Bij de behandeling van patiënten met meerdere chronische aandoeningen zijn huisartsen op dit soort 'enkelvoudige' richtlijnen aangewezen. In het geval van multimorbiditeit kunnen deze ziekte-specifieke richtlijnen de prevalentie van polyfarmacie verhogen en neemt het risico op het voorschrijven van potentiële ongepaste medicatie toe. Nog niet alle factoren die van invloed zijn op polyfarmacie zijn bekend.

In **Hoofdstuk 2** werd de prevalentie van polyfarmacie in een willekeurige steekproef van 1.002 patiënten, tussen de 50 en 80 jaar, in de eerstelijn in Zwitserland bestudeerd. Daarnaast werd de associatie tussen polyfarmacie en comorbiditeit (waaronder cardiovasculaire preventie) in kaart gebracht om subgroepen met een verhoogd risico op polyfarmacie te identificeren.

We vonden een hoge prevalentie van polyfarmacie. In de totale groep (50-80 jaar) had ongeveer 40% polyfarmacie, in de oudste leeftijdsgroep (75-80 jaar) zelfs meer dan de helft. Sommige ouderen kregen zelfs 10 of meer chronische medicijnen voorgeschreven. Patiënten in de oudste leeftijdsgroep met hypertensie hadden een negenvoudig verhoogd risico op polyfarmacie.

Deze studie onderstreept het belang om ieder medicatievoorschrift zorgvuldig af te wegen. Sleutelfactoren hierbij zijn leeftijd, het aantal chronische aandoeningen en het type aandoening (bijv. hypertensie). Huisartsen moeten een gedegen klinische inschatting maken en vervolgens samen in een proces van gezamenlijke besluitvorming ('shared decision-making') met de patiënt beslissen welke medicatievoorschriften gestart, gecontinueerd of gestopt kunnen worden.

Lage SBD is geassocieerd met sterfte en cognitieve achteruitgang bij kwetsbare ouderen met complexe gezondheidsproblemen

Observationele studies hebben aangetoond dat een lage SBD geassocieerd is met cognitieve achteruitgang bij oudere en kwetsbare patiënten met multimorbiditeit en polyfarmacie. Er wordt aangenomen dat de hemodynamische regulatie van het hart en brein verstoort raakt als gevolg van een door intensieve behandeling met antihypertensiva verlaagde bloeddruk en dat dit het cognitief functioneren doet verminderen. Deze hypothese wordt ondersteund door een studie waar in een geselecteerde groep van 80-jarigen met dementie of milde cognitieve stoornissen een verband gevonden werd tussen een lage SBD en slechter cognitief functioneren bij

gebruik van antihypertensiva, terwijl deze associatie zonder het gebruik van antihypertensiva niet gevonden werd. Beperkingen van deze studie waren een kleine steekproefgrootte en de korte follow-up-periode van minder dan een jaar.

Het doel van **Hoofdstuk 3 en 4** was het onderzoeken van de associatie tussen SBD en sterfte, cognitief en dagelijks functioneren en kwaliteit van leven bij de oudere, met antihypertensiva behandelde patiënten. Om de relatie met kwetsbaarheid te onderzoeken werd gestratificeerd voor kwetsbaarheid.

In **Hoofdstuk 3** werd de data van de Leiden 85-plus Studie geanalyseerd, een prospectief populatie-gebaseerd cohortonderzoek waarin 85-jarige inwoners van Leiden (n=599) waren uitgenodigd om deel te nemen. Een lage SBD bij antihypertensiva gebruikers was geassocieerd met een verhoogd risico op sterfte en met versnelde jaarlijkse cognitieve achteruitgang. Echter, kwetsbaarheid gemeten door handknijpkracht had invloed op de associatie met cognitief functioneren. Ouderen met een zwakke handknijpkracht gingen cognitief sneller achteruit, maar dit gold niet voor niet-kwetsbare deelnemers en deelnemers die niet voor hypertensie werden behandeld.

In ISCOPE, een meer recent observationeel cohortonderzoek van 75-plussers (n=1.266) met één jaar follow-up dat beschreven is in **Hoofdstuk 4**, werd dezelfde relatie tussen een lage SBD en versnelde cognitieve achteruitgang bij ouderen die met antihypertensiva werden behandeld bevestigd. In deze studie werd geen negatief effect op het dagelijks functioneren of op de kwaliteit van leven aangetoond. Opnieuw werd de associatie beïnvloed door kwetsbaarheid, hier gedefinieerd als het hebben van complexe gezondheidsproblemen. Bij deelnemers met complexe gezondheidsproblemen was een lage SBD geassocieerd met cognitieve achteruitgang, maar dit gold niet voor deelnemers zonder complexe gezondheidsproblemen. Deze bevinden zijn in overeenstemming met de bevindingen uit de Leiden 85-plus Studie.

Aangezien bovenstaande observationele studies hebben laten zien dat een hogere bloeddruk tijdens de behandeling van hypertensie beter is voor het cognitief functioneren en voor de overleving van oudere patiënten, worden artsen aangemoedigd om een individuele aanpak te hanteren bij de behandeling van hypertensie bij 75-plussers met kwetsbaarheid. Voor een verdere wetenschappelijke onderbouwing van deze behandeling is het belangrijk om nieuwe gerandomiseerde gecontroleerde trials uit te voeren naar de effectiviteit en veiligheid van bloeddrukverlaging bij 75-plussers met kwetsbaarheid.

Variatie in behandeling van hypertensie bij ouderen door huisartsen

Omdat het weinige bewijs dat er is voor de optimale behandeling van hypertensie bij 75-plussers niet eenduidig is, luidde onze hypothese dat er verschillen in behandelstrategie tussen

huisartsen zouden kunnen zijn. In **Hoofdstuk 5 en 6** werd getracht deze verschillen in kaart te brengen, en werd bestudeerd wat de invloed van kwetsbaarheid op de behandeling van hypertensie bij 75-plussers door huisartsen in verschillende landen is. In deze internationale studies werd onderzocht of de verschillen verklaard konden worden door de voor het land specifieke cardiovasculaire ziektelast en levensverwachting.

In deze studie werden 2.543 huisartsen uit 29 verschillende landen in Europa, Brazilië, Israël en New Zeeland met behulp van case-vignetten, allemaal beschreven ze een 80-plusser zoals mevr. S. **Hoofdstuk 5** laat zien dat huisartsen uit verschillende landen hele verschillende beslissingen maakten over de behandeling van hypertensie bij deze patiënten. Het advies om te behandelen varieerde tussen de 34% en 88% per land. Kwetsbaarheid speelde een belangrijke rol in de afweging van huisartsen om met antihypertensiva te starten. In **Hoofdstuk 6** werden de verschillen tussen landen bestudeerd aan de hand van land-specifieke gezondheidsdata, waaronder de cardiovasculaire ziektelast en levensverwachting bij een leeftijd van 60 jaar. In landen met een hoge cardiovasculaire ziektelast waren huisartsen meer geneigd om te starten met antihypertensiva. Deze associatie werd beïnvloed door de land-specifieke levensverwachting voor zestigjaren; hoewel er een positieve associatie was in landen met een lage levensverwachting bij een leeftijd van 60 jaar, werd er geen associatie in landen met een hoge levensverwachting bij een leeftijd van 60 jaar gevonden.

De bevindingen uit **Hoofdstuk 5 en 6** bevestigden de hypothese dat huisartsen hypertensie bij ouderen niet uniform behandelen, en dat patiëntkenmerken, de nationale ziektelast van cardiovasculaire ziekten en levensverwachting een rol in de besluitvorming van de huisarts spelen. Beide studies hebben implicaties voor verder onderzoek en de klinische praktijk. Er is behoefte aan cohortstudies van hoge kwaliteit of (idealiter) nieuwe hypertensie trials waarin kwetsbare patiënten worden geïncludeerd om inzicht te krijgen in de rol van kwetsbaarheid bij de behandeling van hypertensie onder 75-plussers. Ook kwalitatieve studies zouden kunnen helpen om de gevonden variatie beter te begrijpen.

Hoofdstuk 7 vat de belangrijkste bevindingen samen: 1) polyfarmacie komt vaak voor onder ouderen en hypertensie is een van de belangrijke determinant van polyfarmacie; 2) een lage SBD gedurende behandeling met antihypertensiva is geassocieerd met een toename van totale sterfte en cognitieve achteruitgang bij ouderen met kwetsbaarheid; 3) er is veel variatie in de manier waarop huisartsen uit 29 voornamelijk Europese landen besluiten om bij ouderen antihypertensiva te starten. Huisartsen behandelden kwetsbare ouderen minder vaak, maar met name in landen met een lage levensverwachting werd hun beslissing ook beïnvloed door de mate van cardiovasculaire ziektelast in het land.

Deze bevindingen zijn besproken in de context van de huidige literatuur en de casus van mevr. S. Methodologische beperkingen zijn besproken, waaronder de belangrijkste beperkingen van associatie versus causaliteit, omgekeerde causaliteit en "confounding". Als richting voor verder onderzoek worden wetenschappers aangemoedigd om de effectiviteit en veiligheid van het stoppen of verminderen van antihypertensiva ('deprescribing') om de SBD te verhogen in nieuwe trials te onderzoeken bij kwetsbare 75-plussers.

Vanuit een klinisch perspectief wijzen de resultaten van dit proefschrift in de richting van het herdefiniëren van de individuele streefwaarden voor SBD voor kwetsbare ouderen die antihypertensiva gebruiken.

DEUTSCHE ZUSAMMENFASSUNG

ÄrztInnen stehen vor einem Dilemma, wenn sie den optimalen systolischen Blutdruck (SBD) bei älteren PatientInnen über 75-jährig festlegen sollen. Denn diese Menschen zeichnen sich durch grosse Unterschiede aus in Bezug auf kognitive und körperliche Funktionen: Einige sind sehr gesund, andere haben mehrere chronischen Krankheiten (Multimorbidität) und nehmen deswegen regelmässig mehrere Medikamente ein (d.h. haben Polypharmazie) oder sind gebrechlich.

Mit zunehmendem Alter steigt der Blutdruck als Folge der Versteifung der Blutgefässe. Es wurde viel darüber debattiert, ob eine Blutdrucksenkung auch im hohen Alter vorteilhaft ist. Die Meinungen gehen besonders bei über 75-jährigen PatientInnen auseinander, die von Multimorbidität, Polypharmazie und/oder Gebrechlichkeit betroffen sind. Grosse randomisierte Studien konnten zwar zeigen, dass eine Blutdrucksenkung bei über 60-jährigen – und selbst bei über 80-jährigen - Vorteile bringen, indem Herzinfarkt-, Hirnschlag- und Sterberisiko abnahmen. Es gilt jedoch zu beachten, dass solche Studien häufig nicht auf alle PatientInnen übertragbar sind, denn typischerweise werden besonders multimorbide oder gebrechlich PatientInnen davon ausgeschlossen.

Gleichzeitig zeigen Beobachtungsstudien beunruhigende Folgen eines zu tiefen Blutdrucks: Mehrere Kohortenstudien konnten bei über 75-jährigen einen Zusammenhang zwischen tiefem Blutdruck und erhöhtem Sterberisiko und rascherer Abnahme der Kognition zeigen. Trotzdem halten aktuelle Richtlinien die ÄrztInnen an, den Blutdruck bei allen älteren PatientInnen auf Werte unter 130mmHg zu senken. Dies schürte Diskussionen über Nutzen und Risiken, wenn der Blutdruck bei über 75-jährigen mittels blutdrucksenkenden Medikamenten (Antihypertensiva) gesenkt wird. Besonders bei gebrechlichen PatientInnen mit z.B. einem schwachen Händedruck oder komplexen Gesundheitsproblemen, welche in ihrem Alltag stark einschränkt leben.

Kapitel 1 fasst dieses Dilemma anhand eines Patientenbeispiels zusammen. Frau S., eine 90-jährige Frau mit Multimorbidität und Polypharmazie suchte ihren Hausarzt auf um ihren Blutdruck zu messen. Dieser betrug 154mmHg unter Antihypertensiva. Ihr Hausarzt möchte seine PatientInnen durch Antihypertensiva vor Hirnschlag und Herzinfarkt schützen. Gleichzeitig möchte er aber auch ihre kognitive und körperliche Leistungsfähigkeit sowie ihre Lebensqualität erhalten. Frau S. ist eine typische Patientin, die von Blutdruckstudien ausgeschlossen wird. Wir wissen also nicht, ob sich die Ergebnisse von solchen randomisierten Studien auf sie übertragen lassen oder nicht.

Diese Arbeit möchte zum Wissen über die Effekte einer Blutdrucksenkung bei gebrechlichen über 75-jährigen beizutragen. Sie hat drei Ziele: 1. Die Prävalenz von Polypharmazie bei älteren PatientInnen zu bestimmen. 2. Zu testen, ob es einen Zusammenhang gibt zwischen tiefem Blutdruck und Sterblichkeit, kognitiven und körperlichen Leistungsfähigkeit sowie der Lebensqualität bei PatientInnen unter blutdrucksenkender Therapie. 3. Zu verstehen, welche Rolle die Gebrechlichkeit im Entscheid von HausärztInnen aus verschiedenen Ländern spielt, wenn sie darüber entscheiden, ob sie ältere PatientInnen mit Antihypertensiva behandeln. Auch geht es darum zu untersuchen, ob eine länderspezifische Erhöhung von Herzkreislauferkrankungen und die Lebenserwartung die Unterschiede zwischen den Ländern erklären.

Polypharmazie als Folge der Prävention von Herzkreislaufkrankheiten

Die meisten Richtlinien zu chronischen Krankheiten betrachten Krankheiten einzeln und nicht im Zusammenhang mit anderen Krankheiten, an denen PatientInnen gleichzeitig leiden. HausärztInnen müssen sich aber auf Richtlinien verlassen können, um PatientInnen mit mehreren chronischen Krankheiten optimal behandeln zu können. Wenn aber bestehende Richtlinien bei diesen multimorbiden PatientInnen zur Anwendung kommen, steigt das Risiko, dass es im Rahmen einer Polypharmazie zu potentiell nicht angebrachten Medikamenten kommt. Noch immer sind nicht alle Faktoren bekannt, die zu Polypharmazie führen.

In **Kapitel 2** beabsichtigten wir die Prävalenz von Polypharmazie in einer Zufallsstichprobe von 1002 PatientInnen zwischen 50 und 80 Jahren aus Schweizer Polikliniken zu bestimmen. Weiter wollten wir diejenigen PatientInnen identifizieren, die das höchste Risiko für Polypharmazie haben, beispielsweise aufgrund einzelner Krankheiten oder zur Prävention von Herzkreislaufkrankheiten.

Wir fanden eine sehr hohe Prävalenz von 40% aller PatientInnen, welche von Polypharmazie betroffen waren. In der ältesten Gruppe (75-80-jährig) waren es sogar mehr als jeder zweite. Einige PatientInnen nahmen sogar 10 und mehr Medikamente längerfristig ein. Das Risiko einer Polypharmazie war sogar 9-fach erhöht bei älteren PatientInnen mit der Diagnose eines Bluthochdrucks.

Diese Studie unterstreicht die Wichtigkeit, dass jede medikamentöse Verschreibung kritisch hinterfragt werden sollte. Das Alter und die Anzahl chronischer Krankheiten gehören zu den Hauptfaktoren für Polypharmazie, aber genauso die Diagnose von Bluthochdruck. HausärztInnen müssen einen ausgewogenen Entscheid treffen und diesen zusammen mit ihren PatientInnen diskutieren, um festzulegen, welche Medikamente gestartet, weitergeführt, reduziert oder gestoppt werden.

Tiefer Blutdruck steht im Zusammenhang mit Sterblichkeit und Abbau von Kognition bei gebrechlichen PatientInnen mit komplexen Gesundheitsproblemen

Beobachtungsstudien fanden bereits einen Zusammenhang zwischen tiefem Blutdruck und Abbau der Kognition bei älteren, gebrechlichen PatientInnen mit Multimorbidität und Polypharmazie. Es gab Spekulationen darüber ob der tiefe Blutdruck durch Antihypertensiva die hämodynamische Regulation zwischen Herz und Hirn stört und so die Kognition nachhaltig auch gestört wird. Ein Meilenstein stellte dabei eine Studie bei 80-jährigen mit Demenz oder Gedächtnisproblemen. Ein tiefer Blutdruck stand dabei im Zusammenhang mit einem Abbau der Kognition aber nur bei PatientInnen die unter Antihypertensiva standen. Bei PatientInnen ohne blutdrucksenkende Medikamente bestand kein solcher Zusammenhang. Ein Problem der Studie war jedoch, dass sie nur wenige PatientInnen umfasste und diese nur über eine kurze Zeit von weniger als ein Jahr verfolgt wurden.

In **Kapitel 3 und 4** untersuchten wir deswegen ältere PatientInnen mit blutdrucksenkenden Medikamenten auf einen Zusammenhang von Blutdruck, Sterblichkeit, geistiger und körperlicher Leistungsfähigkeit sowie Lebensqualität. Wir untersuchten dabei gebrechliche und nicht-gebrechliche PatientInnen separat.

In **Kapitel 3** untersuchen wir Daten von der Leiden-85-plus Studie, einer Bevölkerungsbezogenen prospektiven Kohortenstudie, wo alle 85-jährigen Bewohner aus Leiden eingeladen wurden und 599 teilnahmen. Bei Menschen unter blutdrucksenkender Therapie, fanden wir einen Zusammenhang zwischen tiefem Blutdruck und erhöhter Sterblichkeit sowie rascherem kognitiven Abbau. Gebrechlichkeit, gemessen mittels Händedruck, veränderte diesen Zusammenhang aber: Wer gebrechlich war, zeigte auch einen vermehrten kognitiven Abbau bei tieferen Blutdruckwerten. Wer einen stärkeren Händedruck besass oder gar nicht mit Antihypertensiva behandelt wurde, zeigte diesen Zusammenhang nicht.

In ISCOPE, einer in **Kapitel 4** beschriebenen jüngeren Kohortenstudie mit über 75-jährigen (n=1266), die über ein ganzes Jahr lang verfolgt wurden, konnten wir erneut dieselben Zusammenhänge bestätigen, jedoch ohne den negativen Effekt auf die Alltagsfunktion und die Lebensqualität. Erneut beeinflusste die Gebrechlichkeit die Resultate, diesmal gemessen daran ob Studienteilnehmer komplexe Gesundheitsprobleme hatten oder nicht. Mit komplexen Gesundheitsproblemen, zeigten die PatientInnen einen beschleunigten kognitiven Abbau, wenn der Blutdruck zu tief war. Wie bei der Leiden-85-plus Studie gab es keinen solchen Zusammenhang bei Teilnehmern ohne Antihypertensiva.

Wir konnten also zeigen, dass höher eingestellte Blutdruckwerte unter Antihypertensiva einen besseren Effekt hatten auf Sterblichkeit und Kognition. Für Ärzte bedeutet dies, bei ihren PatientInnen individuell den Blutdruckzielwert einzustellen. Dies ist besonders wichtig

bei älteren PatientInnen, die gebrechlich und über 75-jährig sind. Für Forscher sehen wir den Nutzen darin, neue randomisierte Studien durchzuführen, um das Absetzen bzw. das Reduzieren (genannt „Deprescribing") von Antihypertensiva bei gebrechlichen über 75-jährigen Menschen auf Nutzen und Sicherheit zu testen.

Unterschiede in der Blutdrucksenkung bei älteren PatientInnen durch HausärztInnen

Weil das Wissen zur optimalen Blutdruckeinstellung bei über 75-jährigen Menschen mangelhaft ist und Studien zu unterschiedlichen Resultaten kamen, vermuteten wir, dass dies auch zu unterschiedlichen Behandlungsabsichten bei HausärztInnen führen könnte. In **Kapitel 5 und 6**, untersuchen wir die Rolle von Gebrechlichkeit, wenn sich HausärztInnen aus verschiedenen Ländern für oder gegen eine Blutdrucksenkung bei über 75-Jährigen entscheiden. Auch untersuchen wir, ob sich diese Unterschiede durch länderspezifische, unterschiedliche Häufigkeiten von Herzkreislauferkrankungen oder Lebenserwartungen erklären liessen.

Die Studie untersuchte 2543 HausärztInnen aus 29 Ländern Europas sowie Brasilien, Israel und Neuseeland. Wir entwickelten Fallbeispiele von Menschen wie Frau S., alle über 80 Jahre alt, und fanden in **Kapitel 5**, dass HausärztInnen bei den gleichen Fallbeispielen je nach Herkunftsland sehr unterschiedlich Antihypertensiva einsetzten. Es gab Länder in denen 34% aller HausärztInnen Blutdrucksenker starten würden und 88% anderen Ländern. Wie vermutet spielte die Gebrechlichkeit eine wichtige Rolle in diesem Entscheidungsprozess.

In **Kapitel 6**, untersuchten wir die gefundenen Länderunterschiede in Bezug auf die Häufigkeit von Herzkreislaufkrankheiten und Lebenserwartung ab 60 Jahren. Es zeigte sich, dass HausärztInnen häufiger eine blutdrucksenkende Therapie starteten in Ländern, wo Herzkreislaufkrankheiten häufiger auftraten. Jedoch nur, wenn in diesen Ländern gleichzeitig auch die Lebenserwartung tiefer war. In Ländern mit vergleichsweise hoher Lebenserwartung behandelten HausärztInnen unabhängig von der Häufigkeit von Herzkreislaufkrankheiten.

Beide Ergebnisse in **Kapitel 5 und 6** bestätigten die Hypothese, dass HausärztInnen den Blutdruck nicht einheitlich im hohen Alter behandeln. Patienteneigenschaften wie auch länderspezifische Unterschiede spielen dabei eine grosse Rolle wie auch im obengenannten Fall von Frau S. Beide Ergebnisse sind von grosser Bedeutung für die Forschung und die Praxis. Wichtig ist es qualitativ hochstehende Kohortenstudien oder (idealerweise) neue randomisierte Blutdruckstudien durchzuführen, die bewusst gebrechliche PatientInnen einschliessen. Damit werden wir in Zukunft besser verstehen, welche Rolle die Gebrechlichkeit in der Behandlung von über 75-jährigen Menschen spielt. In Zukunft sollten Studien auch untersuchen, ob die Anwendung von Richtlinien die gefundenen Unterschiede erklären wie

HausärztInnen Blutdrucksenker einsetzen. Dabei können qualitative Studien helfen, diese Unterschiede besser zu verstehen.

Kapitel 7 fasst die Hauptergebnisse dieser Arbeit zusammen: 1. Polypharmazie ist sehr häufig bei älteren Menschen und eine Diagnose von Bluthochdruck erhöht das Risiko dafür nochmals deutlich. 2. Tiefer Blutdruck steht im direkten Zusammenhang mit einer erhöhten Sterblichkeit und einem rascheren Abbau der Kognition bei älteren gebrechlichen PatientInnen, wenn sie Blutdrucksenker einnehmen. 3. Wie vermutet besteht ein beträchtlicher Unterschied darin, wie HausärztInnen in verschiedenen Ländern blutdrucksenkende Medikamente bei älteren Menschen einsetzen. Bei gebrechlichen PatientInnen wurde der Blutdruck weniger häufig gesenkt. Dieser Entscheid wurde jedoch davon beeinflusst, wie häufig Herzkreislaufkrankheiten in den entsprechenden 29 Ländern auftraten, besonders dort wo eine tiefere Lebenserwartung vorlag.

Weiter diskutierten wir die Resultate unserer Studien im Kontext der bestehenden Literatur und dem Fall von Frau S. Ebenso wurden methodologische Einschränkungen diskutiert wie z.B. die Problematik wann ein Zusammenhang auch wirklich kausal ist und nicht von umgekehrter Kausalität oder „Confounding" erklärt werden könnte. Diese Arbeit hat weitereichende Folgen auf Forschung und Praxis. Sie soll Forscher dazu ermutigen, neue randomisierte Studien durchzuführen, um Nutzen und Sicherheit zu evaluieren, wenn blutdrucksenkende Medikamente bei gebrechlichen über 75-jährigen PatientInnen reduziert oder gestoppt werden, um den Blutdruck wieder zu erhöhen. Für die Praxis empfiehlt sich besonders bei gebrechlichen älteren PatientInnen, die Blutdrucksenker einnehmen ein vorsichtiges Anpassen in Richtung höherer Blutdruckzielwerte.

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CURRICULUM VITAE

Sven Streit was born on September 21 1980 in Aarau, Switzerland. He passed his Gymnasium examination in Aarau in 2001. In 2002, he started medical school at the University of Bern, Switzerland, where he obtained his medical degree and was promoted Dr. med. in 2008. Between 2009 and 2014 he completed his vocational GP training. Sven proudly served as president of the Vasco da Gama Movement (VdGM) in 2011-2012 and the Swiss Association of Young GPs (JHaS) in 2009-2015. During his vocational training in 2012, he started a research fellowship at the Institute of Primary Health Care (BIHAM), at the University of Bern.

In 2015, he began a distant learning Master of Science in Epidemiology program that he completed in 2017 at the London School of Hygiene and Tropical Medicine (LSTHM), United Kingdom. From 2016 to 2017, he received grants from the Swiss National Science Foundation (SNFS) and the Bangerter-Rhyner Foundation for a fellowship to complete his PhD at the Department of Public Health and Primary Care of the Leiden University Medical Center (LUMC), Leiden, the Netherlands. In 2018, he was awarded the *Venia Docendi* (habilitation) in Primary Care and General Internal Medicine by the University of Bern. For the publication presented in Chapter 3 of this thesis, he won the Special Award from the Swiss College of General Practice.

At present, he works part-time as a general practitioner in Konolfingen, Switzerland. At the Institute of Primary Health Care (BIHAM) in Bern, he is Head of Career Development and Networking in Primary Care and continues his clinical research. He is the Principle Investigator of two studies to optimize polypharmacy in older patients with multimorbity, a cluster randomized study funded by the National Research Program 74 of the SNFS, and a project funded by the Swiss General Internal Medicine Foundation about barriers and enablers towards deprescribing in patients and their GPs.