RECOMMENDATIONS FOR TREATMENT OF HYPERTENSION IN THE ELDERLY

Author: Tessa Arlette Landa

Supervisor: Dr. Vita Lesauskaite

Kaunas 2018
TABLE OF CONTENTS

1. SUMMARY ..................................................................................................................3
2. ACKNOWLEDGEMENTS ..............................................................................................4
3. CONFLICTS OF INTEREST .........................................................................................4
4. ABBREVIATIONS ..........................................................................................................5
5. INTRODUCTION .............................................................................................................6
6. AIM AND OBJECTIVES ...............................................................................................7
7. LITERATURE REVIEW: RESEARCH METHODOLOGY AND METHODS ..................8
8. RESULTS AND THEIR DISCUSSION ............................................................................9
  8.1 BLOOD PRESSURE MONITORING ........................................................................9
    8.1.1 DIAGNOSIS OF HYPERTENSION .................................................................9
      8.1.1.1 ORTHOSTATIC HYPOTENSION OR HYPERTENSION ...........................9
      8.1.1.2 POST-PRANDIAL HYPOTENSION ....................................................10
      8.1.1.3 PSEUDOHYPERTENSION ....................................................................10
      8.1.1.4 WHITE-COAT HYPERTENSION .......................................................10
    8.1.2 FOLLOW-UP OF HYPERTENSION TREATMENT ......................................11
      8.1.2.1 HOME BLOOD PRESSURE MONITORING .....................................11
      8.1.2.2 AMBULATORY BLOOD PRESSURE MONITORING ..........................13
  8.2 BLOOD PRESSURE GOAL .......................................................................................16
  8.3 LIFESTYLE MODIFICATION RECOMMENDATIONS ..........................................20
      8.3.1 SODIUM INTAKE RECOMMENDATION ...............................................20
      8.3.2 WEIGHT LOSS RECOMMENDATIONS ...............................................21
      8.3.3 PHYSICAL ACTIVITY RECOMMENDATIONS ......................................22
      8.3.4 DIET RECOMMENDATIONS ...................................................................23
  8.4 PHARMACOLOGICAL RECOMMENDATIONS ....................................................24
      8.4.1 ANTIHYPERTENSIVE DRUG THERAPY ...............................................24
      8.4.2 DRUG INTERACTIONS ............................................................................26
      8.4.3 UNCONTROLLED HYPERTENSION ....................................................26
9. CONCLUSIONS ...........................................................................................................28
10. PRACTICAL RECOMMENDATIONS .........................................................................29
11. REFERENCES ............................................................................................................30
1. SUMMARY

Author name: Tessa Arlette Landa

Research title: Recommendations for treatment of hypertension in the elderly.

Aim: To review general recommendations on hypertension treatment in the elderly.

Objectives:
1. Describe different recommendations for a good blood pressure control in the elderly.
2. Find specific non-pharmacological and pharmacological recommendations.

Methodology: This was a literature review on hypertension in old age by searching electronically in The Medline (PubMed), ResearchGate, Google Scholar and Cochrane Library for studies and guidelines published in the last twenty years (1997–2017).

Results: Diagnosing hypertension in the elderly, pseudohypertension and white-coat hypertension should be considered. Orthostatic hypotenison has been related with a higher risk of mortality and cardiovascular events, as well as falls and syncope. An association of post-prandial hypotension with an increased risk of mortality was found. Evidence suggests that less blood pressure decline during night, non-dipping, is related with a higher cardiovascular risk, however other studies defend that night-time blood pressure rather than dipping status has better correlation with outcome. Leiden-85 plus study, found an association between higher blood pressure values and less physical and cognitive decline at age 85. Moreover, this study also found that with diastolic blood pressure <70 mmHg there was an accelerated decline of renal function. Hypertension in the very elderly trial compared active treatment vs. placebo in patients older than 80 years old. Active treatment reduced cardiovascular events and all-cause deaths. Investigating lifestyle modifications, a large randomized controlled trial found that with sodium restriction there was a reduction in blood pressure. However, hyponatremia has been related with a higher mortality risk. Dietary approaches to stop hypertension clinical trial showed a reduction of blood pressure with a diet rich in vegetables and fruits, and low in saturated and total fat content.

Conclusions: In older adults systolic blood pressure should not reach values below 130 mmHg and diastolic below 60 mmHg. Hypertension should be diagnosed in at least two separate office visits, performing orthostatic test. White-coat hypertension and pseudohypertension need to be considered. With lifestyle recommendations in the elderly, benefits and risks have to be balanced due to higher probability of cognitive decline and/or physical disability. Pharmacological therapy should be started when non-medicamental measures are not effective to reach blood pressure goal. Benefits and side effects have to be considered. Attention to drug treatment compliance should be paid and efforts made to increase it.
2. ACKNOWLEDGEMENTS

I would like to thank Dr. Vita Lesauskaite for her advice and help throughout this final master thesis.

3. CONFLICTS OF INTERESTS

The author reports no conflicts of interests during this study.
4. ABBREVIATIONS

BP- Blood pressure

SBP- Systolic Blood Pressure

DBP- Diastolic Blood Pressure

HYVET- Hypertension in the Very Elderly Trial

ABPM- Ambulatory blood pressure measurement

HBPM- Home blood pressure measurement

ESH/ESC- European Society of Hypertension and European Society of Cardiology

ACE inhibitors- Angiotensin converting enzyme inhibitors

TONETrial of nonpharmacological interventions in the elderly

DASH- Dietary approaches to stop hypertension

BMI- Body mass index
5. INTRODUCTION

Blood pressure, especially systolic blood pressure, increases with age, leading to a high prevalence of hypertension in the elderly [1]. Hypertension is related with target organ damage [2], and is the most common modifiable risk factors for conditions such as atherosclerosis, stroke, heart failure, atrial fibrillation, diabetes mellitus, sudden cardiac death, acute aortic syndromes, chronic kidney disease, and may lead to death and disability [3].

The prevalence of hypertension appears to be around 30–45% in general population [4], and as the population is aging prevalence of hypertension is increasing [3].

Ischemic heart diseases and stroke remain the top two causes of death in Lithuania [5].

Many times there is uncertainty about management of hypertension in the older adults [3]. Treatment of hypertension in the elderly is challenging because of multiple comorbidities, polypharmacy, cognitive impairment, orthostatic hypotension, variable life expectancy, and frailty [6].

Blood pressure monitoring out-of-the office is especially important in the elderly [7]. Conditions such as white-coat hypertension, masked hypertension [7], orthostatic hypotension, increased risk of adverse effects of hypotension, increased blood pressure fluctuations during the day [8] and nocturnal hypertension [9], make blood pressure monitoring challenging and necessary.

In the treatment of hypertension in the elderly, different recommendations of blood pressure goal can be found through studies of large randomized controlled trials [10-12]. Special attention has been focused lately on different adverse events caused by very low blood pressure. There are new studies showing that very low blood pressure may lead to greater cognitive decline [13], kidney damage [14], decreased myocardial perfusion [15] and an increased risk of mortality [16].

Other challenges in treatment management are non-pharmacological recommendations, such as lifestyle changes. Different lifestyle changes are proven to decrease blood pressure, but elderly are generally less represented in clinical trials, less advised to modify lifestyle habits and less eager to do this [3].

As pathophysiology of hypertension changes with age together with pharmacokinetics and pharmacodynamics, antihypertensive medication effect could be different in older than younger individuals [3]. Some studies defend the view that the same effects are seen in all individuals throughout age [17], however, according to other studies some antihypertensive drugs should be avoided in the elderly [18].

As new studies are emerging related to specific management of hypertension in the elderly, we review general recommendations specific to the older adults to optimize blood pressure and decrease adverse events in this population.
AIM AND OBJECTIVES

AIM:

To review general recommendations during hypertension treatment in the elderly, as not many studies are focused on the treatment of high blood pressure in older age we follow a literature review to summarize different recommendations that are specific to the elderly.

OBJECTIVES:

1. Describe different recommendations to reach a good blood pressure control in the elderly.
2. Find specific non-pharmacological and pharmacological recommendations.
7. RESEARCH METHODOLOGY AND METHODS

Guidelines for the management of hypertension were identified by searching The Medline (PubMed) keywords: “hypertension”, “elderly” and “guideline”. To use the most recent guidelines, we focused on guidelines published between January 2010 and December 2017. Relevant studies were found by cited references in guidelines. In addition, to find more relevant studies we searched electronically in The Medline (PubMed), ResearchGate, Google Scholar and Cochrane Library for studies published in the last twenty years (1997–2017) using the keywords “hypertension,” “elderly”, “recommendations”, “antihypertensives”, “treatment”, “blood pressure”, “control”, “ambulatory blood pressure”, “compliance”, “lifestyle” and “electronic devices”.

Exclusion criteria compromised the following:

1. Studies only in younger individuals
2. Comorbidities such as kidney failure, chronic kidney disease, heart failure, myocardial infarction, stroke, diabetes mellitus, gout, Alzheimer, dyslipidemia.

Following the further inclusion and exclusion criteria explained above, 55 articles were selected for the present review.
8. RESULTS AND THEIR DISCUSSION

8.1 BLOOD PRESSURE MONITORING

8.1.1 DIAGNOSIS OF HYPERTENSION

Blood pressure (BP) should be correctly measured and recorded to diagnose hypertension [3]. For the diagnosis of hypertension 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend taking at least 2 different blood pressure measurements throughout the office visit, allowing the patient to sit for 3–5 minutes before recording any BP value. If the first 2 values are quite different between them, additional measurements should be taken [4]. According to a peer-reviewed article on hypertension in the elderly, diagnosis of hypertension should be based on BP measurements taken on at least 2 separate office visits in order to evaluate the variability of BP and other factors that may affect BP [3].

8.1.1.1 ORTHOSTATIC HYPOTENSION OR HYPERTENSION

BP should be measured after standing for 1 min and 3 min to evaluate orthostatic hypotension or hypertension [3]. Orthostatic hypotension, defined as a reduction in systolic blood pressure (SBP) of \( \geq 20 \) mmHg or in diastolic blood pressure (DBP) of \( \geq 10 \) mmHg within 3 min of standing, is more common in older adults [19] and has been related with an increased risk of mortality and cardiovascular events [4] as well as falls and syncope [3]. With age, baroreflex function decreases and there is an increase in venous insufficiency which both lead to a higher incidence of orthostatic hypotension in the elderly. On the other hand, orthostatic hypertension is also common in the elderly and should be evaluated [3].
8.1.1.2 POST-PRANDIAL HYPOTENSION

Furthermore, it is recommended to record BP after a meal to evaluate presence of post-prandial hypotension [3]. Post-prandial hypotension has been associated with a higher risk of mortality. A prospective cohort study selected 179 semi-independent residents aged 65 and older to evaluate which indices of BP are the stronger predictor of mortality. Of all the participants at baseline, 47% had hypertension, 38% post-prandial hypotension, and 23% orthostatic hypotension. Over 4.7 years, those who died were more likely to have post-prandial hypotension. The study concluded that post-prandial hypotension could be an independent predictor of all-cause mortality [20]. Moreover, there are special conditions in the elderly that could lead to inaccurate blood pressure measurement as pseudohypertension and white-coat hypertension [3,21].

8.1.1.3 PSEUDOHYPERTENSION

When arteries are excessively stiffened they may not collapse with inflation of the BP cuff and can lead to a falsely high SBP, referred as pseudohypertension. With age the brachial arteries tend to become stiffened due to arterial medial sclerosis and calcification, and when BP is measured using indirect techniques, for example a sphygmomanometer, it can be falsely increased. According an American Expert Consensus Document on hypertension when pseudohypertension may be suspected, as in individuals with refractory hypertension, no organ damage and/or symptoms of overtreatment, direct intra-arterial measurement for the diagnosis of hypertension should be used [3].

8.1.1.4 WHITE-COAT HYPERTENSION

The other source of inaccurate BP measurement values, especially in the elderly, is white-coat hypertension. One should suspect white-coat hypertension when BP measured in a clinical setting is elevated compared to a normal BP measured out of the office. According to several studies it is far more prevalent in the elderly compared to younger individuals [3, 4,22,23]. A cross-sectional study with 9550 participants, from which 1408 were between 60 and 70 years old and 719 were 70 years old or higher, studied the association between the age of the patients and BP values measured in the office and out of the office. Out of the office values were measured by daytime ambulatory blood pressure measurements (ABPM). The prevalence of white-coat hypertension exponentially increased from the youngest group to those aged ≥70 years. The office BP values in
individuals aged ≥60 years were significantly higher than daytime ambulatory BP values (5.0 and 13.0 mm Hg for systolic; 2.0 and 4.2 mm Hg for diastolic BP) [24].

In patients with office hypertension but no organ damage, grade 1 hypertension in the office or at low cardiovascular risk, 2013 ESH/ESC Guidelines recommend to confirm white-coat hypertension or diagnosis of hypertension by ABPM [4].

When assessing BP in the elderly we recommend considering white-coat hypertension and pseudohypertension. Detecting white-coat hypertension and pseudohypertension is important to avoid antihypertensive overtreatment [23]. When excessive BP reduction occurs in the elderly it may lead to symptomatic hypotension which can affect treatment compliance [8] and cause severe side effects, as syncope and falls, increased cognitive decline [13], a faster decline in renal function [14] and other complications, such as decreased myocardial and brain perfusion [16]. These complications will be further explained in part 2, blood pressure goal.

To diagnose hypertension we recommend to measure correctly BP in at least 2 separated office visits, to make orthostatic test and assess BP after a meal. If white-coat hypertension or pseudohypertension is suspected we recommend using appropriate techniques in both conditions to make a proper diagnosis.

8.1.2 FOLLOW-UP OF HYPERTENSION TREATMENT

Once the diagnosis of hypertension is made, a proper follow-up is recommended. Hypertension diagnosis and follow-up is primarily based on BP values recorded in the physician’s office [7, 25]. However, several features in the elderly make monitoring BP out of the office especially important.

8.1.2.1 HOME BLOOD PRESSURE MONITORING

Self-measurement of blood pressure at home in the elderly prospective cohort study in France compared the prognostic value of home vs. office BP measurements in elderly treated hypertensives, 4939 individuals were included with an average age of 70 years. From those 4939 individuals, there was a prevalence of 42% of masked hypertension, defined as a controlled office BP but high home BP values. The individuals with masked hypertension had a higher cardiovascular risk compared to those with low BP in and out of the office and the elderly with white-coat hypertension, who only had a slight increase in cardiovascular risk. The study concluded that home blood pressure measurements
(HBPM) has a better prognostic value than office BP measurement and recommend that all treated hypertensives should be monitored by HBPM [26].

2010 European Guidelines of Home blood pressure monitoring also recommend HBPM in all treated hypertensives, especially in those more likely to have masked hypertension as patients 60 years old or more with high normal systolic office BP, male patients older than 70 years or smokers. According to this guideline there are three features in the elderly which make HBPM important [8]. First, high prevalence of white-coat hypertension as explained above. Second, older adults tend to have higher fluctuations of BP during the day which could be related to higher cardiovascular risk. And third feature, in the elderly auto-regulation of the target organs circulation during hypotension could be impaired. Antihypertensive medication according to office BP values could cause an excessive BP reduction with symptomatic hypotension and cause severe side effects with falls, syncope, increased cognitive decline and others as we will further explain in point 2. HBPM can prevent overtreatment due to white-coat hypertension, undertreatment in patients with masked hypertension, detect severe BP reduction during hypertension treatment, improve long term control and further features listed in table 1.

However, it may be difficult to use HBPM in many elderly due to physical and cognitive disabilities [3, 8] and/or may be contraindicated in patients with anxiety or obsessive behavior. Diaries with recordings of their self-measured BP can be less reliable due to subjective errors or mistakes in measuring BP. Memory-equipped devices and/or telemonitoring are preferred in this specific population, however they are nonreimbursable costs that lead to an expensive management. Furthermore, oscillometric techniques cannot measure BP in patients with arrhythmias, including atrial fibrillation which is a condition common in the elderly with hypertension [3].

When HBPM cannot be considered, then ABPM for out-of-office values can be used. ABPM is considered as the reference for out-of-office BP and is indicated when discrepancies occur between home and office BP values [4].
### Table 1. Advantages and disadvantages of home blood pressure monitoring[14]

<table>
<thead>
<tr>
<th>Advantages of home blood pressure monitoring</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment initiation</strong></td>
<td></td>
</tr>
<tr>
<td>Detection of white-coat hypertension</td>
<td>Requires patients’ education and training</td>
</tr>
<tr>
<td>Detection of masked hypertension</td>
<td>Requires medical supervision</td>
</tr>
<tr>
<td><strong>After treatment initiation</strong></td>
<td></td>
</tr>
<tr>
<td>Assessment of antihypertensive drug efficacy</td>
<td>May cause anxiety due to random BP fluctuation</td>
</tr>
<tr>
<td>Assessment of duration of antihypertensive drug action</td>
<td>Some patients may make self-adjustment of drug treatment</td>
</tr>
<tr>
<td>Detection of excessive BP-lowering effect of treatment</td>
<td></td>
</tr>
<tr>
<td>Avoidance of overtreatment due to white-coat hypertension</td>
<td></td>
</tr>
<tr>
<td>Avoidance of undertreatment due to masked hypertension</td>
<td></td>
</tr>
<tr>
<td>Evaluation of resistant hypertension</td>
<td></td>
</tr>
<tr>
<td>Improvement of patients’ compliance with treatment</td>
<td></td>
</tr>
<tr>
<td>Assessment of long-term hypertension control</td>
<td></td>
</tr>
<tr>
<td>Improvement of hypertension control rates</td>
<td></td>
</tr>
<tr>
<td>Potential reduction of health-care costs</td>
<td></td>
</tr>
</tbody>
</table>

8.1.2.2 AMBULATORY BLOOD PRESSURE MONITORING

ABPM indications can be seen in table 2 and advantages and disadvantages compared with HBPM in table 3.

One of the indications is to measure BP at night, as ABPM gives information about nighttime blood pressure [4]. During the night, BP tends to decline [27]. According to 2013 ESH/ESC guidelines nocturnal BP is within normal range if the average of nighttime values is below 120/70 mmHg, when values are higher than 125/75 mmHg they are considered abnormal [4].

Nocturnal BP has been of growing interest since in 1988 O’Brien et al. reported that individuals with a less decline of BP during the night had an increased risk of stroke. They came up with terms dipping and non-dipping, non-dipping being less BP decline at night [9].

Careful attention should be done on interpreting high nighttime BP values with ABPM, as repeated cuff-inflation could lead to sleep deprivation and increase BP overnight [28].

Increasing evidence suggests that nocturnal BP is a better predictor of cardiovascular disease outcomes [28] and that patients with less BP decline at night, non-dipping, have a higher cardiovascular risk compared to those with greater BP decline [4].
According to 2013 ESH/ESC guidelines “the most consistent findings about dipping is that in patients with less BP decline at night there is a higher cardiovascular risk compared to those with greater BP decline” [4].

Non-dipping status has been related with higher cardiovascular risk, sleep apnea, obesity, hypertensive target organ damage and metabolic disorders [27].

However, extreme dippers may have an increased risk of stroke but data still remain inconsistent [4]. A meta-analysis, which included 25856 hypertensives from prospective cohort studies and 9461 individuals from randomly selected population samples, evaluated the association between outcome and nocturnal BP level, the night-day BP ratio and dipping status by ABPM. Hansen et al. concluded that in both groups night-time BP was a better predictor of outcomes rather than day-time BP, day-night BP ratio and dipping status [9].

Moreover, a meta-analysis in Europe studied the prognostic significance of day-time and night-time ambulatory BP. After analyzing 4 prospective studies, Fagard et al. concluded that nighttime BP is a better predictor of outcome, and that night-day BP ratio predicts mortality [29].

A cross-sectional study analyzed if dipping and non-dipping patterns were related to organ damage in untreated hypertensive patients with nocturnal hypertension. 343 patients were included with untreated essential hypertension, subclinical organ damage and nocturnal hypertension. All patients underwent two ABPM for 24-h within 4 weeks, as well as cardiac and carotid ultrasonography and 24-h urine collection for microalbuminuria. No correlation was found between the grade of BP fall at night and markers of organ damage. They concluded that with nocturnal hypertension, dippers and non-dippers had similar subclinical organ damage [27].

Results still remain inconsistent about the significance and predictive value of day-night BP ratio, and dipping or non-dipping patterns. However, nocturnal hypertension has been related with increased risk of cardiovascular events and should be carefully monitored by ABPM.

For a good BP control we recommend ABPM and/or HBPM based on patients’ preference, indications, costs, availability and ease of use. We should keep in mind that out-of-office BP recording is especially important in the elderly to maintain a correct follow-up due to higher risk of undertreatment, overtreatment and severe side effects.
Table 2. Indications for home blood pressure monitoring or/and ambulatory blood pressure monitoring[4]

<table>
<thead>
<tr>
<th>Clinical indications for HBPM or ABPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suspicion of white-coat hypertension</td>
</tr>
<tr>
<td>o Grade 1 hypertension in the office</td>
</tr>
<tr>
<td>o High office BP in individuals without asymptomatic organ damage and at low total cardiovascular risk</td>
</tr>
<tr>
<td>• Suspicion of masked hypertension</td>
</tr>
<tr>
<td>o High normal BP in the office</td>
</tr>
<tr>
<td>o Normal office BP in individuals with asymptomatic organ damage or at high total cardiovascular risk</td>
</tr>
<tr>
<td>• Identification of white-coat effect in hypertensive patients</td>
</tr>
<tr>
<td>• Considerable variability of office BP over the same or different visits</td>
</tr>
<tr>
<td>• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension</td>
</tr>
<tr>
<td>• Identification of true and false resistant hypertension</td>
</tr>
</tbody>
</table>

**Specific indications for ABPM**

| • Marked discordance between office BP and home BP |
| • Assessment of dipping status |
| • Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, chronic kidney disease, or diabetes |
| • Assessment of BP variability |

Table 3. Advantages and disadvantages of ambulatory and home blood pressure[7]

<table>
<thead>
<tr>
<th></th>
<th>Ambulatory BP</th>
<th>Home BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of white-coat hypertension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Detection of masked hypertension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assessment of nocturnal BP and dip</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Assessment of morning hypertension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assessment of antihypertensive drug action</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assessment of duration of drug action</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Long-term follow-up of hypertension</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Improvement of patients’ compliance</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Improvement of hypertension control rate</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prognostic value</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Availability</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
8.2 BLOOD PRESSURE GOAL

High BP throughout young and old age is related to vascular mortality, BP should be kept as low as possible to reduce cardiovascular risks [30]. However, the extent to which high BP should be reduced in persons aged 65 or older remains controversial [15].

With increasing age, autoregulation in target organs can be impaired and excessive BP reduction could lead to inefficient target organ perfusion [31]. Sufficiently high BP may be necessary to assure adequate cardiac and cerebral perfusion [16].

This association between high BP and adequate cerebral perfusion could be supported by the Leiden 85-plus study, which found a relationship between higher BP values and less physical and cognitive disability at age 85 [13]. It supported the hypothesis that with increasing age higher BP levels might be needed to ensure perfusion in critical organs due to advanced arterial stiffness. With hypotension, regulatory mechanism in the brain cannot effectively keep enough blood flow, leading to a decline in cerebral perfusion. Therefore, individuals with hypotension in this longitudinal study had the strongest association with increased cognitive decline.

According to the Leiden-85 plus study on the effect of blood pressure on renal function in the elderly, an association was found between low DBP and a faster decline in renal function. Those with DBP <70 mmHg had an accelerated decline of creatinine clearance compared with those with DBP between 70 and 79 mmHg and higher [14].

Low DBP could be a marker of increased risk of death [32]. Specifically, since most myocardial blood flow occurs in diastole, low DBP could also be a strong determinant of decreased myocardial perfusion and possibly cardiovascular mortality [15]. Therefore, in the elderly, DBP should be closely monitored and cautiously reduced as it could challenge critical organ perfusion.

Furthermore, interesting differences can be found on recommendations about hypertension treatment in the elderly between the 2017 American [6] and 2013 European, ESH/ESC guidelines [4]. American guideline recommendations can be further seen in table 4 and European guideline recommendations in table 5.

The American guidelines recommend for older adults (≥65 years of age) with hypertension and multiple comorbidities and limited life expectancy a team-based approach for deciding the intensity of BP lowering. On the other hand, ESH/ESC guidelines recommend leaving decisions on hypertension treatment to the physician alone. In individuals younger than 80 years old if they are fit and treatment is well tolerated ESH/ESC guidelines recommend a treatment target of SBP lower than 140 mmHg and American guidelines recommend a further decrease in SBP, with a treatment target under 130 mmHg.
In individuals older than 80 years old in good physical and mental condition, ESH/ESC guidelines recommend to reduce SBP between 150 and 140 mmHg, however American guidelines recommend the same approach as individuals younger than 80 years old, SBP < 130 mmHg.

**Table 4. Recommendations for treatment of hypertension in older persons [6]**

<table>
<thead>
<tr>
<th>Recommendations for Treatment of Hypertension in Older Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment of hypertension with a SBP treatment goal of less than 130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥ 65 years of age) with an average SBP of 130 mmHg or higher.</td>
</tr>
<tr>
<td>2. For older adults (≥ 65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.</td>
</tr>
</tbody>
</table>
Focusing on SBP and on large randomized controlled trials and analysis of these trials, different outcomes are seen [15, 10-12,33,34].

Hypertension in the Very Elderly Trial (HYVET) consisted of a trial that followed individuals with hypertension (SBP ≥160 mmHg) older than 80 years comparing active treatment vs. placebo to study the outcomes of high BP treatment in octogenarians. The trial was stopped before expected time due to a reduction in cardiovascular events and all-cause deaths in the active treatment group by a SBP goal of <150 mmHg [11]. Active treatment in octogenarians could be beneficial according HYVET, but mean SBP reached in the active treatment group was 144 mmHg, in consequence after this trial questions were raised if even further decrease in SBP would be beneficial for the very old.

Vantaa study in Finland investigated the association between BP in individuals >85 years old and survival over 9 years, in individuals with a SBP below 140 mmHg and an increased risk of mortality was seen [16].

In 65 years or older individuals, different studies have compared intense (SBP <140 mmHg) vs. moderate (SBP <150 mmHg) antihypertensive therapy with different results according benefits and

---

**Table 5. Antihypertensive treatment strategies in elderly [4]**

<table>
<thead>
<tr>
<th>Antihypertensive treatment strategies in the elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td>In elderly hypertensives with SBP ≥160 mmHg:</td>
</tr>
<tr>
<td>o Recommended reducing SBP to between 150 and 140 mmHg</td>
</tr>
<tr>
<td>In fit elderly patients &lt;80 years old antihypertensive treatment:</td>
</tr>
<tr>
<td>o May be considered at SBP values ≥140 mmHg with a target SBP &lt;140 mmHg if treatment is well tolerated</td>
</tr>
<tr>
<td>In individuals older than 80 years with an initial SBP ≥160 mmHg:</td>
</tr>
<tr>
<td>o Recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions</td>
</tr>
<tr>
<td>In frail elderly patients:</td>
</tr>
<tr>
<td>o Recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment</td>
</tr>
<tr>
<td>Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian</td>
</tr>
<tr>
<td>All antihypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension</td>
</tr>
</tbody>
</table>

---
side effects. Two Japanese trials comparing more vs. less intense BP lowering treatment in the elderly could not show increased benefits from lowering SBP to 136 and 137 mmHg rather than 145 and 142 mmHg [12, 33].

Furthermore, a meta-analysis evaluated the outcomes of intensive BP treatment in individuals who were 65 years or older and it was found a 29% decrease of mayor adverse cardiovascular events with intensive BP lowering (<140mmHg) but with a probable increased risk of renal failure [34].

A subgroup of elderly individuals in the Felodipine Event Reduction study, a double-blind randomized trial who included young and old individuals in a Chinese population, showed a reduction of 25-35% in cardiovascular events by lowering SBP just below 140 mmHg, reaching a mean SBP of 138 mmHg, compared to 142 mmHg [10].

A Spanish cohort study in individuals aged 65 years and older found a higher risk of mortality with systolic blood pressure <115 mmHg [15].

According to these studies we do not recommend treatment targets of systolic blood pressure lower than 130 mmHg, as no additional benefit has been found in the elderly. Drastic lowering of SBP should be avoided, as a Spanish study showed an increased risk of mortality when SBP reaches values lower than 115 mmHg. We also recommend a team-based approach to decide the best treatment of each individual with a special consideration for those individuals >65 years old who are frail and suffering from multiple morbidities and living in nursing homes.
8.3 LIFESTYLE MODIFICATION RECOMMENDATIONS

Hypertension could be prevented by lifestyle modification and lifestyle changes can even be the only treatment necessary in milder forms of hypertension in all age groups, including the elderly. Lifestyle changes to decrease BP include moderate sodium intake reduction, diet rich in fruits and vegetables, weight reduction if necessary, physical activity and moderate alcohol consumption [3]. Sodium intake restriction and weight reduction has been proven to decrease BP by several randomized clinical trials and shown by meta-analysis [3,4,35,36].

8.3.1 SODIUM INTAKE RECOMMENDATION

A large randomized controlled trial evaluated the effect of sodium and weight reduction in 975 individuals between 60 and 80 years old receiving treatment with one antihypertensive drug with BP lower than 145/85 mmHg. From all participants, 585 were obese. Patients were randomly assigned to usual care, or weight reduction (in obese), sodium restriction, or both. After 3 months from the beginning of the trial, withdrawal of antihypertensive drug was attempted. In those patients assigned to salt restriction, there was a 20 mEq/day decrease in sodium excretion and those assigned to weight reduction, had an average weight reduction of 3.5-4.5 kg. Compared to usual care, the reduction in BP in salt restriction group was 2.6/1.1 mmHg, in weight loss group 3.2/0.3 mmHg, and with combined therapy 4.5/2.6 mmHg. The primary endpoint of the trial was defined as presence of high BP at 1 or more study visit after an attempted withdrawal of antihypertensive drug, treatment with an antihypertensive drug, or a cardiovascular disease complication during follow-up. These primary endpoints at 30 months were less often with salt restriction, weight reduction and combined salt restriction and weight reduction, than in usual care group. This study concluded that with dietary lifestyle changes, BP can be decreased reducing the need of antihypertensive drugs in the elderly [35]. However, older patients may have some trouble following the dietary salt restriction advice as they tend to be more depended in processed packaged foods, higher in salt amount compared to fresh food, and they may consume more salt to compensate for the decreased taste sensitivity [3]. Furthermore, elderly have a higher risk to develop hyponatremia, a serum sodium concentration <136 mmol/L [37]. Hyponatremia has been related with a higher mortality risk [38]. The symptoms of acute hyponatremia, such as vomiting, nausea, coma or stupor, and chronic hyponatremia, including fatigue, cognitive impairment, gait disorders, falls and fractures, are more common and severe in the elderly [challenges and solutions]. Severe hyponatremia complications include cerebral edema due to acute hyponatremia, and osmotic demyelination when correcting chronic hyponatremia too rapid [37]. However, mild hyponatremia, serum sodium concentration 131 ± 3 mmol/L, has been related with
adverse events especially in the elderly. In older individuals with mild or moderate hyponatremia, attention and postural balance may be more affected than in younger individuals [39].

A prospective population-based cohort study evaluated the association between mild hyponatremia, bone fractures, bone mineral density, falls and fractures. The study included 5208 individuals with a mean age of 70.3 ± 9.1 years that had data of serum sodium concentration at baseline. They concluded that elderly with mild hyponatremia were at higher risk of having fractures. However, no relation was found with recent fall [37].

Caution should be done on advising sodium restriction in the elderly due to risk of severe side effects. We recommend advising moderate sodium restriction and to follow-up the patient for possible side effects. Sodium intake should be moderately reduced to no more than 100 mEq/day (2.4 g sodium or 6 g sodium chloride) [3].

8.3.2 WEIGHT LOSS RECOMMENDATIONS

Increased body weight is associated with hypertension [4]. The randomized controlled trial mentioned above showed that with weight reduction in obese patients there is a decrease in BP. 2013 ESH/ESC guidelines recommend maintaining a body mass index (BMI) about 25 kg/m2 and a waist circumference of 102 cm in men and 88 cm in women. However, the optimal BMI is unclear. In patients with cardiovascular disease symptoms some observational data suggested that there is a worse prognosis following weight loss, including the elderly [4]. An analysis of 57 prospective studies concluded that mortality was lowest at a BMI of 22.5-25 kg/m2 [40]. On the other hand, a systematic review and meta-analysis concluded that grades 2 and 3 obesity was associated with higher mortality and mortality was lower in overweight individuals [41]. Therefore, weight reduction in the elderly should be done carefully and not with a BMI goal as low as with adults and young individuals.
8.3.3 PHYSICAL ACTIVITY RECOMMENDATIONS

Physical activity is another lifestyle recommendation to decrease or prevent high blood pressure. Physical inactivity is considered as a cardiovascular risk factor [42].

A cohort study evaluated the grade of exercise capacity and mortality risk in male veterans 70 years or older with hypertension. 2154 male veterans were included and according to their exercise capacity they were divided in 4 fitness categories. Faselis et al. concluded that there was an inverse, independent and graded association between exercise capacity and mortality risk in hypertensive individuals aged ≥70 years [42].

A study evaluated endurance, circuit and relaxing training in 40 elderly participants with clinically diagnosed grade 1 hypertension. Resting BP and quality of life were evaluated, among other factors, before and after 12 weeks of endurance, circuit or relaxing training. Resting BP was significantly reduced by 11% in all 3 groups of training. Quality of life was also improved. The study concluded that relaxing training could be used as an alternative in old individuals unable or reluctant to perform endurance or circuit training [43].

A study analyzing different approaches in treatment of elderly found significant reduction in falls, an increase speed in walking, a better ability to perform activities of daily living and reduced hospitalization rates and physician visits in elderly with increased physical activity or after trials of endurance or resistance exercise in elderly with falls or frailty [44].

According to Canadian physical activity guidelines all healthy adults aged 65 years or older should perform at least 150 min of moderate to vigorous-intensity aerobic physical activity per week, in periods of 10 min or more, and at least 2 days per week of muscle- and bone-strengthening exercise. Those with poor mobility should enhance balance with physical activities to prevent falls. For those who are frail or have a disability, they should do physical activity according to their limits and risks [45].

Physical activity should be advised in the elderly adjusted to their own limitations and balancing their benefits and risks, as it has been proven to decrease blood pressure and increase their quality of life and reduce amount of falls.
8.3.4 DIET RECOMMENDATIONS

Another lifestyle change proven to decrease BP is a diet rich in fruits, vegetables, whole-grains, poultry, fish, and nuts, low in sweets, sugar-sweetened beverages and red meats [3,4,6]. It is a diet with reduced saturated and total fat and low-fat dairy products. Referred as Dietary Approaches to Stop Hypertension (DASH) diet.

According to American guidelines lifestyle management proven to decrease BP is a diet rich in fruits, vegetables, low-fat dairy products and reduced in saturated and total fat. [3,36]

A clinical trial, DASH, included 459 adults with SBP less than 160 mmHg and DBP between 80 and 95 mmHg. Individuals were selected randomly to different diet regimens to evaluate their effect on BP: a control diet, a diet rich in vegetables and fruits, or a combination diet. Control diet was low in fruits, vegetables and dairy products and the combination diet, rich in fruits and vegetables with low-fat dairy products and reduced saturated and total fat content. The combination diet reduced SBP by 5.5 mmHg and DBP by 3.0 mmHg more than the control diet. The diet rich in fruits and vegetables reduced SBP by 2.8 mmHg and DBP by 1.1 mmHg more than the control diet. The combination diet, referred now as DASH diet, can substantially reduce BP [46].

The American guidelines of lifestyle recommends DASH diet to older adults, as well as European guidelines. These guidelines defend that this diet should be accompanied by other lifestyle changes. A further decrease in BP is seen when combining DASH diet with exercise and weight loss [4] as well as with sodium reduction [47].

Moreover, Mediterranean diet has been associated with a decreased risk of cardiovascular diseases compared to northern European countries and the United States. It consists of a diet with high intake of extra-virgin olive oil, vegetables including leafy green vegetables, fruits, nuts and legumes, cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals [54].

A randomized controlled diet performed in Spain enrolled 7447 persons who where at high cardiovascular risk into three different diets, a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet advised to reduce dietary fat. A median follow up of 4.8 years was performed. Estruch et al. concluded that a Mediterranean diet with supplemented extra-virgin olive oil or nuts decreased the incidence of major cardiovascular events [55].

When recommending lifestyle changes in the elderly, benefits and risks should be evaluated due to higher risk of cognitive decline and physical disability. Exercise should be recommended with caution, together with moderate sodium restriction and DASH or Mediterranean diet. Restrictive diets should not
be recommended to avoid malnourishment. Weight loss in obese grade 2 and 3 patients should be encouraged.

**8.4 PHARMACOLOGICAL RECOMMENDATIONS**

### 8.4.1 ANTIHYPERTENSIVE DRUG THERAPY

According to 2013 ESH/ESC guidelines, pharmacological therapy should be started when lifestyle changes are not enough to reach BP goal [4]. 2013 ESH/ESC guidelines recommend initiation or maintenance of antihypertensive treatment with diuretics, calcium antagonists, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers as monotherapy or in combination [4]. There are physiological changes with aging that may affect drug absorption, distribution, metabolism and excretion that could lead to an increased or decreased drug effect. Pharmacokinetic variation with aging and drugs affected with these changes can be found in table 6.

*Table 6. Pharmacokinetic changes with aging of antihypertensive drugs [3]*

<table>
<thead>
<tr>
<th>Process</th>
<th>Physiological change</th>
<th>Result</th>
<th>Drugs affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Reduced gastric acid production</td>
<td>Reduced tablet dissolution and decreased solubility of basic drugs</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Reduced gastric emptying rate</td>
<td>Decreased absorption for acidic drugs</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Reduced gastrointestinal motility, gastrointestinal blood flow, and absorptive surface</td>
<td>Less opportunity for drug absorption</td>
<td>--</td>
</tr>
<tr>
<td>Distribution</td>
<td>Decreased total body mass; increased proportion of body fat</td>
<td>Increased volume of distribution of highly lipid-solube drugs</td>
<td>Beta blockers, central alpha agonists</td>
</tr>
<tr>
<td></td>
<td>Decreased proportion of body water</td>
<td>Decreased volume of distribution of hydrophilic drugs</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Decreased plasma albumin, disease-related increased alpha1-acid glycoprotein, and altered relative tissue perfusion</td>
<td>Changed perfect of free drug, volume of distribution, and measured levels of bound drugs</td>
<td>Propanol</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Reduced liver mass, liver blood flow, and hepatic metabolic capacity</td>
<td>Accumulation of metabolized drugs</td>
<td>Propanolol, diltiazem, labetalol, verapamil</td>
</tr>
<tr>
<td>Excretion</td>
<td>Reduced glomerular filtration, renal tubular function, and renal blood flow</td>
<td>Accumulation of renally cleared drugs</td>
<td>ACE inhibitors, atenolol, sotalol, nadolol</td>
</tr>
</tbody>
</table>
When prescribing antihypertensive drug therapy, changes mentioned in table 6 have to be evaluated and drug dosage adjusted individually for every patient according to their condition. A meta-analysis on randomized controlled trials studied the effect of different antihypertensive drug groups on major cardiovascular events within 2 age groups, <65 vs. ≥65 years. The study concluded that different drug groups did not have substantial difference in protection of cardiovascular events within age groups. However, most individuals were between 50 and 80 years old and individuals outside this range were mostly not represented. This analysis could not show the effects of different antihypertensives in the oldest old group [17].

A trial of nonpharmacological interventions in the elderly (TONE), studied the association between quality of life and different BP lowering drug classes. 975 individuals were included within 60 and 81 years without any major disease and disability treated for hypertension with antihypertensive medication, with a BP of < 145/85 mm Hg. TONE study concluded that benefits for patients treated with diuretics, beta blockers, calcium channel blockers and ACE inhibitors were similar but beta blockers increased depressive symptoms [35].

Moreover, a meta-analysis from randomized controlled trials evaluated the effect of beta blockers in preventing cardiovascular events as first line therapy in hypertension. It separated trials including older patients, ≥ 60 years, from those including younger patients, <60 years. As pathophysiology of hypertension can be different in older and younger groups, this study wanted to compare response of beta blockers between different age groups. In placebo-controlled trials and active comparatory trials, beta blockers did not decrease risk of cardiovascular events in the older patients compared to younger patients where the risk decreased. Khan et al. concluded that this drug group should not be indicated as first line therapy in the elderly if no other indications exist for these agents [18]. Beta blockers should be indicated in elderly with hypertension if they suffer another condition such as heart failure, coronary artery disease, migraines, certain arrhythmias, headaches or senile tremor [3].

Furthermore, diuretics and calcium channel blockers are indicated as first-line therapy in elderly with isolated systolic hypertension [4].

From the group of diuretics, thiazides are generally indicated as initiating therapy in the elderly. However, they may lead to orthostatic hypotension and electrolyte disturbances, as hypokalemia, hyponatremia or hypomagnesemia which may increase arrhythmias. Thiazides frequently lead to hyponatremia, which is a severe adverse event in elderly as explained in part 3. When used, serum potassium and sodium levels should be closely monitored. Potassium-sparing diuretics, mineralocorticoid antagonists, and epithelial sodium transport channel antagonists can be indicated as combination therapy with another antihypertensive drug[3].
Calcium channel blockers are well tolerated in the elderly. They act by blocking influx of calcium ions into the cells of vascular smooth muscle and myocardial tissue being more effective in coronary and peripheral arterial smooth muscle than in cardiac and skeletal muscle. Therefore, not rigorously affecting myocardial contractility or skeletal muscle [3].

8.4.2 DRUG INTERACTIONS

Before starting antihypertensive drug therapy possible drug interactions of patient’s drug prescriptions should be analyzed. Medications that increase BP, including NSAIDS, corticosteroids, erythropoietin, amphetamine, ergotamine and anabolic steroids, should be checked for the possibility of being removed or substituted with another medication before initiating drug therapy. Especially in the older adults, as the average elderly takes > 6 prescription drugs [3].

8.4.3 UNCONTROLLED HYPERTENSION

Once therapy is started but BP goal is not reached, before starting with a new antihypertensive drug, possible causes of uncontrolled hypertension should be checked. One of the possible causes of uncontrolled hypertension is drug interactions. Therefore as explained above, thorough examination of patient’s drug prescription should be done before initiating another antihypertensive. Insufficient compliance is other possible cause related to uncontrolled hypertension, however it remains underestimated [48].

A prospective study evaluated patients’ adherence to antihypertensive therapy, Cheng et al. found that from 821 individuals who participated only 37% reported consistent adherence to their antihypertensive treatment [49].

Older age and asymptomatic state of hypertension have been related with a higher risk of noncompliance [50].

Different methods to increase compliance have been studied. A common factor found in adherent patients is the perception of a low health status; in non-adherent patients they frequently stopped treatment due to feeling well without medication [3]. Patients’ education could lead to an increased compliance and better controlled hypertension.

Furthermore, in the elderly, polypharmacy and high cost of medications can cause a lower BP control. High cost of medications is of high concern in the elderly due to generally lower incomes and use of many medications [3]. Is recommended to prescribe generic and formulary drugs if possible.
A systematic review analyzed the association between treatment compliance and dose regimens in studies where they only used electronic monitoring to report compliance. 76 studies were included. For once-daily regimens compliance was significantly higher than for 3 or 4-times daily and twice-daily than for 4-times daily. Claxton et al. concluded that there is an inverse relationship with the number of pills taken and the compliance rate, less frequent regimens resulted in better adherence to treatment [51].

Therefore, trying to minimize daily dosages in treatment regimens of the patients leads to better adherence rates. According Aronol et al. “use of once-daily drug formulations provides a significant improvement in compliance to a prescribed regimen and may improve outcomes” [3].

Burnier et al. selected a group of 41 patients with refractory hypertension to monitor adherence to treatment with a micro-electronic monitor. After 2 months, 30% of patients had hypertension controlled as a result of monitoring. A subgroup of patients with low adherence continued with the study and achieved a further control of BP [48].

Moreover, HBPM can increase treatment compliance [3,4], one of the advantages of using HBPM included in table xx in part 1.

Traditional methods to report compliance, such as pill counting, questionnaires, patients’ diaries and others, have shown to overestimate adherence. New technologies are being created to increase compliance when taking drugs. Such as monitors that automatically record the date and time of each opening of the medication container [52].

A randomized controlled trial including 68 uncontrolled hypertensives individuals evaluated adherence over a 12-month period. They were assigned into 2 different groups. One group, defined as usual care, with drugs dispensed as usual. The second, as intervention group, with drug adherence monitored by an electronic system, medication event monitoring system. The target BP was more likely to be reached in the intervention group, monitored by the electronic system, as patients increased their compliance with the electronic medication container [53].

However, patients may open the box without taking any pill or taking another dose than prescribed, reporting by mistake a good adherence [52]. Furthermore, the effect may decrease over time [53].
9. CONCLUSIONS

1. Blood pressure in adults older than 65 years old, in good physical condition, should reach values between 130-150 mmHg for systolic blood pressure and diastolic blood pressure between 70-90 mmHg. In older adults systolic blood pressure should not reach values below 130 mmHg and diastolic below 60 mmHg. For individuals who are frail and suffering from multiple comorbidities, a team-based approach is recommended.

2. Hypertension should be diagnosed in at least two separate office visits, performing orthostatic test. White-coat hypertension and pseudohypertension need to be considered.

3. With lifestyle recommendations in the elderly, benefits and risks have to be balanced due to higher probability of cognitive decline and/or physical disability.

4. Pharmacological therapy should be started when non-medicamental measures are not effective to reach blood pressure goal. Benefits and side effects have to be considered. Attention to drug treatment compliance should be paid and efforts made to increase it.
10. PRACTICAL RECOMMENDATIONS

1. Hypertension in older adults should be diagnosed in at least two separate office visits, performing orthostatic test.
2. In older adults systolic blood pressure should not reach values below 130 mmHg and diastolic below 60 mmHg.
3. When recommending lifestyle changes in the elderly, benefits and risks should be evaluated due to higher risk of cognitive decline and physical disability. Exercise should be recommended with caution, together with moderate sodium restriction and DASH or Mediterranean diet. Restrictive diets should not be recommended to avoid malnourishment.
11. REFERENCES


