Awareness, Treatment and Control of Hypertension in Austria

Doctoral thesis at the Medical University of Vienna for obtaining the academic degree

Doctor of Philosophy

Submitted by

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Declaration

The present work was carried out at the 3rd Medical Department, Cardiology and Intensive Care Medicine, Wilhelminenhospital, Vienna.

Peer-reviewed funding was granted by the Health Insurance Fund of Lower Austria (Niederösterreichische Gebietskrankenkasse, NÖGKK) and the initiative ‘Tut Gut’ of a public health panel of Lower Austria (Niederösterreichischer Gesundheitsausschuss, NÖGUS)

As integral aspect of this study, patient recruitment was carried out at pharmacies in Lower Austria.
Table of Contents

Declaration ........................................................................................................................................ ii
List of Figures ................................................................................................................................... v
List of Tables .................................................................................................................................... vii
Abstract in English ........................................................................................................................ viii
Abstract in German ....................................................................................................................... ix
Publications Arising from the Thesis .......................................................................................... x
Abbreviations .................................................................................................................................. xi
Acknowledgments ........................................................................................................................ xii
1  Introduction ............................................................................................................................. 1
  1.1 General Introduction ............................................................................................................. 1
  1.2 Hypertension – A Multifactorial Disease .......................................................................... 2
    1.2.1 Pathogenesis ............................................................................................................... 2
    1.2.2 Diagnoses of Hypertension ....................................................................................... 9
    1.2.3 Treatment of Hypertension ...................................................................................... 10
  1.3 Hypertension Control – Available Data in Austria .......................................................... 25
  1.4 Available Data in Europe and the United States ............................................................. 26
    1.4.1 Prevalence of Hypertension ..................................................................................... 26
    1.4.2 Awareness, Treatment and Control ......................................................................... 27
  1.5 Aims of the Thesis ............................................................................................................. 30
2  Results ....................................................................................................................................... 31
  2.1 Prologue .............................................................................................................................. 31
  2.2 PDF of First Paper .............................................................................................................. 32
3  Discussion .................................................................................................................................. 42
List of Figures

Figure 1-1 **Hypertension – a multifaceted disease.** Adapted from Johnson et al., Oparil et al. and Carretero et al. 14,45,82

Figure 1-2 **The association of cardiovascular outcome events and the percentage of blood pressure reduction.** Reductions in cardiovascular outcome events are proportional to the reductions of systolic blood pressure, diastolic blood pressure and pulse pressure, without differences between the types of blood pressure. Due to the logarithmic association, risk reduction increases to a progressively smaller extent the larger the blood pressure reduction become. Legend: D-BP: blood pressure difference; CHD: coronary heart disease; HF: heart failure; CV: cardiovascular (Reprinted from Zanchetti et al. with permission of the publisher. Copyright ©2014, Wolters Kluwer Health, license details can be found in the Appendix 94).

Figure 1-3 **Relative and absolute risk reduction of cardiovascular outcome events in trials of blood pressure lowering.** A, Intentional blood pressure lowering trials. B, Intentional blood pressure lowering trials exclusively in hypertensive patients. C, Intentional and nonintentional blood pressure lowering trials together. Blood pressure lowering significantly reduces the risk for various cardiovascular outcome events, with particularly strong effect for the reduction of stroke and heart failure. Standardised risk ratio (RR) is to a systolic/diastolic blood pressure difference of 10/5 mmHg. Legend: HT: hypertension; CHD: coronary heart disease; HF: heart failure; CV: cardiovascular (Reprinted from Zanchetti et al. with permission of the publisher. Copyright ©2014, Wolters Kluwer Health, license details can be found in the Appendix 94).

Figure 1-4 **Absolute risk reduction by antihypertensive treatment, standardised to a systolic/diastolic blood pressure reduction of 10/5 mmHg, and residual risk for outcome events stratified by cardiovascular risk in the control group.** Blood pressure lowering was associated with greater absolute risk reduction in patients at higher baseline risk for cardiovascular events. Also,
a higher atherothrombotic risk profile carried a higher residual risk for cardiovascular events when blood pressure lowering fails. Legend: CHD: coronary heart disease; HF: heart failure; HR: high risk; LMR: low-moderate risk; VHR: very high risk; VVHR: very very high risk (Reprinted from Zanchetti et al. with permission of the publisher. Copyright ©2014, Wolters Kluwer Health, license details can be found in the Appendix 94).

Figure 1-5 First-line treatment for hypertension and preferred combinations. Adopted from Mancia et al. 103

Figure 1-6 Marked decrease in diastolic blood pressure after surgical sympathectomy. Reprinted from Longland et al. with the permission of the publisher, Copyright ©1954 John Wiley and Sons, license details can be found in the Appendix 127

Figure 1-7 Long-term survival of patients undergoing splanchnicectomy versus medical treatment for essential hypertension. Legend: BP: blood pressure. Adopted from Smithwick et al. 128

Figure 1-8 Dinamap blood pressure measurements of a patient during a hypertensive crisis. The authors observed a strong decline in systolic and diastolic blood pressure during device stimulation. After deactivation of the device, blood pressure recovered over 4 hours. Reactivation of the device repeatedly resulted in a blood pressure drop. Reprinted from Mohaupt et al. with permission of the publisher. Copyright ©2007, Wolters Kluwer Health, license details can be found in the Appendix 141

Figure 1-9 Hypertension control rates in Europe and North America. References: Canada: McAlister et al. 153; USA: Egan et al. 151; France, UK, Spain, Greece, Austria (2010): Banegas et al. 10; Germany: Neuhauser et al. 158; Italy: Tocci et al. 159; Austria (2003): Hitzenberger et al. 12; Bangladesh: Rahman et al. 160

Figure 3-1 Key actions to improve blood pressure control identified by a group of international experts. Legend: HT: hypertension; BP: blood pressure. Reprinted from Redon et al. with permission of the publisher. Copyright ©2016, Wolters Kluwer Health, license details can be found in the Appendix 167
List of Tables

Table 1-1  **The Aetiology of Hypertension.** Adapted from Oparil et al. 14

Table 1-2  **Classification of office blood pressure levels.** Adapted from Mancia et. al. 83

Table 1-3  **Classification of out-of-office based blood pressure levels.** Adopted from Mancia et. al. and Quinn et al. 83 92

Table 1-4  **Blood pressure thresholds as recommended by different guidelines** 83 103 105-107

Table 1-5  **Preferred antihypertensive substance classes for different clinical conditions.**

Abstract in English

Background
Arterial hypertension (HTN) is the single largest contributor to mortality world-wide, however, adequate blood pressure (BP) control is achieved in less than half of diagnosed and treated patients. Since recent data are lacking in Austria, we sought to assess BP control in predominantly adherent patients who were medically treated for HTN.

Methods and Results
In a cross-sectional study, 4,303 patients suffering from HTN and who visited one of 158 participating pharmacies in order to obtain their antihypertensive medication were enrolled. Recruitment was performed within a period of 10 consecutive days in October 2015. Average systolic and diastolic BP was 144±20/84±12 mmHg under treatment with 2.2±1.1 different antihypertensive substances. Forty-five percent received a modern single-pill combination drug. Awareness for the disease was found in 93%, and 90% claimed to be compliant to medication intake on the day of study participation. In total, 41% achieved the BP target of 140/90 mmHg.
Lower age (OR 0.90, 95% CI 0.85, 0.96 per decade increase), self-reported medication compliance at study participation (OR 2.15, 95% CI 1.67, 2.76), an academic degree (OR 1.58, 95% CI 1.19, 2.08), female gender (OR 1.23, 95% CI 1.07, 1.41) and treatment by a specialist vs. a family doctor (OR 1.20, 95% CI 1.04, 1.39) were major predictors of BP control.

Conclusion
In a cohort of predominantly adherent patients treated for HTN, only 41% achieved the BP target. Given the low number of antihypertensive drugs prescribed, physician’s inertia might be at least partly accountable for these results.
Abstract in German

Hintergrund
Arterielle Hypertonie ist der bedeutendste singuläre Risikofaktor für die Gesamtsterblichkeit weltweit, wobei weniger als die Hälfte aller diagnostizierten und behandelter Patienten das Blutdruckziel erreichen. Da in Österreich keine rezenten Daten verfügbar sind, war es Ziel der Studie die Blutdruckkontrolle in vorwiegend therapietreuen Patienten zu untersuchen.

Methoden und Ergebnisse
Im Durchschnitt betrug der systolische/diastolische Blutdruck 144±20/84±12 mmHg unter Therapie mit 2.2±1.1 verschiedenen antihypertensiven Substanzen. Fünfundvierzig Prozent wurden mit einem modernen Kombinationspräparat behandelt. Die Awareness für die Erkrankung lag bei 93%, und 90% der Teilnehmer konstatierten die blutdrucksenkende Medikation am Studientag eingenommen zu haben. In Summe erreichten 41% normotensive Blutdruckwerte unter 140/90 mmHg.
Niedrigeres Alter (OR 0.90, 95% CI 0.85, 0.96 pro Dekade Anstieg), Einnahme der blutdrucksenkenden Therapie am Studientag (OR 2.15, 95% CI 1.67, 2.76), ein akademischer Studienabschluss (OR 1.58, 95% CI 1.19, 2.08), weibliches Geschlecht (OR 1.23, 95% CI 1.07, 1.41) und eine Gestaltung der antihypertensiven Therapie durch einen Facharzt vs. einem Hausarzt (OR 1.20, 95% CI 1.04, 1.39) waren mit dem Erreichen des Blutdruckziels assoziiert.

Zusammenfassung
In einer Kohorte von überwiegend therapietreuen Patienten welche aufgrund einer arteriellen Hypertonie in Behandlung standen, erreichten nur 41% das Blutdruckziel. Aufgrund der niedrigen Anzahl an verschriebenen Antihypertensiva muss die Trägheit des Arztes zur Therapieintensivierung als ursächlicher Faktor in Betracht gezogen werden.
Publications Arising from the Thesis

Rohla M, Haberfeld H, Tscharre M, Huber K, Weiss TW.

Awareness, treatment, and control of hypertension in Austria: a multicentre cross-sectional study.

J Hypertens 2016;34(7):1432-40
Abbreviations

ABPM: ambulatory blood pressure measurement
ACEI: angiotensin converting enzyme inhibitor
AOBP: automated office blood pressure measurement
ARB: angiotensin receptor blocker
BAT: baroreceptor activation therapy
BB: beta blocker
BP: blood pressure
CCB: calcium channel blocker
CHD: coronary heart disease
CHEP: Canadian Hypertension Education Program
CV: cardiovascular
CVD: cardiovascular disease
DBP: diastolic blood pressure
eGFR: estimated glomerular filtration rate
ENaC: epithelial sodium channel
ESC: European Society of Cardiology
ESH: European Society of Hypertension
HBPM: home blood pressure measurement
HF: heart failure
HTN: hypertension
NCC: sodium-chloride cotransporter
RAS: renin-angiotensin-system
RDN: renal denervation
SBP: systolic blood pressure
SOP: standard operating procedure
US: United States
WHC: white coat hypertension
Acknowledgments

Firstly, I would like to acknowledge my supervisors Professor Thomas Weiss and Professor Kurt Huber for their tremendous support throughout these years. With their guidance and trust they allowed me to follow my interests in cardiovascular research. I could not have asked for more liberty or more opportunities to promote my career in an independent manner. At the same time they always provided a helping hand and brilliant advice when needed.

I would also like to thank Heinz Haberfeld and the team of the Pharmacists College of Lower Austria for their excellent support during the conduct of the study, and particularly for encouraging 158 colleagues to participate. To date, the study is one of the largest conducted in the field of hypertension in Austria, carried out with great commitment on behalf of the Pharmacists College. It was a true pleasure to work with the team around Heinz Haberfeld.

I would also like to thank all participating pharmacists and co-workers who willingly contributed to the study, and did so with an amount of precision and reliability which I have rarely witnessed when working with other parties.

Lastly I would like to thank my family and friends who always encouraged me.
1 Introduction

1.1 General Introduction

In western countries, one out of three deaths can be attributed to cardiovascular disease (CVD).\textsuperscript{1} Although therapeutic advances have reduced cardiovascular mortality, the high morbidity represents one of the main challenges for health authorities today.

Public campaigns and novel legislation that address the primary prevention of CVD have been shown to be effective, for example by reducing the extent of tobacco use.\textsuperscript{2} However, other risk factors for CVD are still inadequately addressed. Hypertension (HTN) is one of the most prominent risk factors for a variety of severe and costly diseases, such and stroke, heart failure and myocardial infarction with consequent disability, chronic kidney disease and dementia.\textsuperscript{3,4} In particular, elevated blood pressure (BP) is the single largest contributor to mortality globally, responsible for 13\% of all deaths world-wide.\textsuperscript{5,6} In the USA and across European countries approximately 30-65\% of the adult population suffers from HTN.\textsuperscript{7,8}

Despite the substantial and obvious burden of the disease, adequate BP control is achieved in only 30-50\% of patients in Europe.\textsuperscript{9,10}

In Austria, representative data collected in the late 1990 demonstrated dramatically low HTN control rates, and little efforts have been made to investigate the quality of BP management since.\textsuperscript{10-12} We sought to close this gap in evidence by providing representative data on awareness, treatment and control of HTN.
1.2 Hypertension – A Multifactorial Disease

1.2.1 Pathogenesis

Essential, or primary HTN is present in 90-95% of cases, suggesting that moncausal aetiologies such as primary hyperaldosteronism, hyperthyroidism, renal artery stenosis or pheochromocytoma are infrequent in a general population. Accordingly, essential HTN resembles a condition secondary to a complex interplay between genetic, environmental, demographic and clinical factors (Figure 1-1). The following, partly complementary mechanisms have been discussed to be involved in the development and progression of the disease (Table 1-1):

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Greater similarity of BP within vs. between families, independent of the environment</td>
</tr>
<tr>
<td>Adoption studies, greater concordance between biological than adoptive siblings</td>
<td>Biron et al. Can Med Assoc J 1976;115(8):773-4</td>
</tr>
<tr>
<td>Sympathetic nervous system</td>
<td>Stimulation of cardiac output, peripheral resistance and fluid retention</td>
</tr>
<tr>
<td>Autonomic imbalance, reduced parasympathetic tone, and elevated heart rate correlating with BP</td>
<td>Kim et al. Hypertension 1999;33(2):640-6</td>
</tr>
<tr>
<td>Alteration in chemoreflex pathways in response to apnea or hypoxia</td>
<td>Somers et al. Hypertension. 1988;11: 608-12</td>
</tr>
<tr>
<td>Renal sympathetic stimulation increased in hypertensive vs. normotensive individuals</td>
<td>Heran et al. Cochrane Database Syst Rev. 2012 Aug 15;8:CD004643</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Peripheral vascular resistance increased through structure and mechanical properties of arterioles (rarefaction, narrowing of the lumen)</td>
<td>Mulvany et al. Physiol Rev. 1990 Oct;70(4):921-61</td>
</tr>
<tr>
<td>Treatment with ACE-inhibitors, angiotensin receptor blockers and calcium channel blockers improve resistance vessel structure</td>
<td>Schiffrin et al. Curr Opin Nephrol Hypertens. 2001 Sep;10(5):617-24</td>
</tr>
<tr>
<td>Increase in SBP and pulse pressure with age through reduced elasticity, arteriosclerosis, collagen deposition, thinning of elastin fibres in the media and smooth muscle cell hypertrophy of large arteries</td>
<td>Zieman et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005; 25: 932-943</td>
</tr>
<tr>
<td>Increased wall thickness due to endothelial dysfunction and reduced NO synthesis</td>
<td>Wilkinson et al. Hypertension. 2004; 44: 112-116</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Effects of angiotensin II&lt;br&gt;-) direct peripheral vasoconstriction (increase in intracellular calcium through G-protein coupled mechanism)&lt;br&gt;-) renal vasoconstriction&lt;br&gt;-) Dipsogenesis&lt;br&gt;-) Stimulation of antidiuretic hormone release&lt;br&gt;-) Aldosterone release&lt;br&gt;-) Increased renal sodium reabsorption</td>
<td>Tzamou et al. J Hum Hypertens. 2013 Sep;27(9):535-8</td>
</tr>
<tr>
<td>Effects of aldosterone&lt;br&gt;-) stimulation of mineralocorticoid receptors in the distal tubule and collecting duct, upregulation of sodium/potassium exchangers&lt;br&gt;-) upregulation of epithelial sodium channels (ENaCs) in the collecting duct&lt;br&gt;-) upregulation of sodium-chloride cotransporters (NCC) in the distal tubule&lt;br&gt;-) potassium secretion into the tubular lumen&lt;br&gt;-) sodium reabsorption in the intestine, salivary and sweat glands</td>
<td>Yusuf et al. N Engl J Med. 2000 Jan 20;342(3):145-53</td>
</tr>
<tr>
<td>HOPE trial: 20% relative reduction of cardiovascular death, myocardial infarction or stroke with ramipril vs. placebo in high-risk patients</td>
<td>Dahlöf et al. Lancet. 2002 Mar 23;359(9311):995-1003</td>
</tr>
<tr>
<td>LIFE trial: 13% relative reduction in death, myocardial infarction or stroke with losartan vs. atenolol in patients with essential hypertension and left ventricular hypertrophy</td>
<td>Williams et al. Lancet. 2015 Nov 21;386(10008):2059-68</td>
</tr>
<tr>
<td>PATHWAY-2 trial: Spironolactone superior in BP lowering vs. bisoprolol, doxazosin and placebo in patients with treatment resistant HTN</td>
<td></td>
</tr>
</tbody>
</table>

Table 1-1 The Aetiology of Hypertension. Adapted from Oparil et al. 14
Johnson and co-workers have sub-summarised the above mentioned evidence into three (primary renal) mechanisms for HTN.\textsuperscript{45}

1.2.1.1 Glomerular Filtration Rate Dependent Hypertension
Firstly, a glomerular filtration-rate dependent, or in other words, a renoprival mechanism was postulated based on the strong correlation between impaired kidney function and HTN.\textsuperscript{46} Animal models demonstrated a rapid development of HTN upon kidney removal or injury.\textsuperscript{45,47} Correspondingly, the prevalence of HTN in humans correlates well with estimated glomerular filtration rate (eGFR), even at a level of mild dysfunction.\textsuperscript{45,48} As mechanistic explanation, a subsequent sodium retention, dysfunctional tubular sodium handling and volume expansion secondary to reduced kidney function was suggested.\textsuperscript{49} In turn, these processes seem to be related to the sympathetic nervous system, thus, release of vasoconstrictors, and the loss of vasodepressor substances.\textsuperscript{45,49,50}

1.2.1.2 Hypertension and Ion Transport Mechanisms
In 1955, Jerome W. Conn, an American endocrinologist, described several cases of HTN secondary to aldosterone-secreting tumors.\textsuperscript{51} Consequently, the impact of sodium handling independent of Conn’s Syndrome was subject to extensive research. The stimulation of mineralocorticoid receptors in the distal tubule and collecting duct, the upregulation of sodium/potassium exchanger, epithelial sodium channels (ENaCs), sodium-chloride cotransporters (NCCs), and the extra-renal sodium reabsorption through the intestine, salivary glands and sweat glands were discovered.\textsuperscript{41} Additionally, it has been shown that obesity seems to increase aldosterone release through epoxy-keto derivates of linoleic acid, which might be elevated in some obese individuals with primary HTN.\textsuperscript{52,53} Worth mentioning, impaired sodium handling in more proximal parts of the nephron can be compensated for in the collecting duct, whereas conditions affecting the final level of regulation, thus, essentially the collecting duct itself, are likely to have the strongest effects on the development of HTN. These hypotheses are supported by a number of rare genetic mutations that affect aldosterone metabolism: The glucocorticoid remedial syndrome, an autosomal-dominant mutation, is associated with an abnormally high rate of aldosterone synthesis. The syndrome of apparent mineralocorticoid excess results in aldosterone-like effects of elevated local concentrations of cortisol in the kidney.\textsuperscript{54}
At the same time, there is evidence that certain G-protein polymorphisms affect the epithelial sodium channel located in the collecting duct, potentially accounting for a major portion of world-wide variation in BP.\textsuperscript{55} Recently, the PATHWAY 2 trial demonstrated that spironolactone (a mineralocorticoid receptor antagonists) had the strongest effects on BP lowering in patients with resistant HTN, compared to bisoprolol, doxazosin and placebo.\textsuperscript{44}

\subsection*{1.2.1.3 Hypertension and Renal Ischemia}

The pathogenesis of HTN is multifaceted in the majority of patients. As mentioned before, HTN can be associated with, or occur secondary to a reduction in glomerular filtration rate, but most patients suffering of HTN have a normal or mildly reduced renal function.\textsuperscript{48} The evidence for genetic factors is similarly compelling, while some studies suggested that genetics might only account for 20\% of HTN variance.\textsuperscript{45, 56-57} However, the strong increase in the prevalence of HTN in Europe and the USA cannot be explained by the latter two mechanisms, pointing towards a strong environmental influence.\textsuperscript{58-60} Predisposing factors that are linked to the increasing cardiovascular morbidity in the western world, including vasoconstriction, oxidative stress and inflammation, need to be considered as well.\textsuperscript{45, 60}

In particular, renal vasoconstriction at the afferent arteriole, mediated by oxidative stress, thromboxane, nitric oxide deficiency and angiotensin II have been suggested to be one, perhaps unifying, initiating mechanism.\textsuperscript{61-65} The engagement into this pathway has been shown to substantially depend on sympathetic overdrive, activation of the renin-angiotensin system and endothelial dysfunction along with impaired nitric oxide synthesis, allowing vascular lesions to develop.\textsuperscript{45, 66-68} Associated with these vascular lesions, an inflammatory response and subsequent infiltration with T-cells and macrophages occurs, further enhancing the release of oxidants and angiotensin II.\textsuperscript{64, 67-69}

From a population-based perspective, the question arises how these contributors to HTN have experienced such an exponential rise in the past decades. A potential acquired component driving this process is the dramatic increase in in the prevalence of obesity. Obesity affected less than 5\% of the adult US population in the 19\textsuperscript{th} century, whereas today the prevalence is above 30\%.\textsuperscript{70} A similar, but somewhat less pronounced trend could be observed in Europe.\textsuperscript{60, 71, 72} Obesity has been shown to be associated with many of the above mentioned mechanisms promoting HTN on a pathophysiological level, including insulin and leptin resistance, sympathetic overdrive, endothelial dysfunction, and aldosterone excess.\textsuperscript{53, 73} Additionally, dietary factors, e.g. increasing fructose consumption, might cause microvascular injury, tubulointerstitial inflammation and elevated uric acid levels.\textsuperscript{74, 75} Uric acid levels have been
shown to affect nitric oxide levels, to inhibit adipokines and to stimulate pro-inflammatory pathways involving C-reactive protein and angiotensin II release.\textsuperscript{76-79}

In line with these findings, a strong association of uric acid levels and the increasing prevalence of obesity and HTN has been reported, once more pointing towards a contributing role of environmental factors.\textsuperscript{80} Lastly, the exposure to high-salt diets has been suggested as another major player involved in the increasing occurrence of HTN in western countries.\textsuperscript{81}
Figure 1-1 Hypertension – a multifaceted disease. Adapted from Johnson et al., Oparil et al. and Carretero et al.
1.2.2 Diagnoses of Hypertension

Although the relationship between elevated BP and CVD incidence is continuous, a classification based on cut-off values is required for practical considerations. Supported by overwhelming clinical trial evidence, the currently established office-based cut-off value is 140/90 mmHg, as recommended by the 2013 European Society of Cardiology (ESC) / European Society of Hypertension (ESH) Guidelines on the Management of Arterial Hypertension (Table 1-2). Lowering BP below this threshold is generally accepted to be beneficial in the overwhelming majority of the population.83

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

Table 1-2 Classification of office blood pressure levels. Adapted from Mancia et al. 83

Due to the shortcomings of office based BP measurements, out-of-office measurements (home BP measurements, HBPM; ambulatory BP measurements, ABPM; automated office BP measurements, AOBP) are increasingly incorporated into guidelines and clinical trials. The diagnosis based on a single office-based measurement in no longer acceptable.83 84 As major advantage, these out-of-office based methods can provide series of data in a non-medical environment, yielding higher reproducibility and accuracy. In particular, white coat hypertension (WHC), present in up to 30-40% of individuals, represents a major drawback of office-based BP measurements.85 86 More recently, automated office BP (AOBP) was introduced into the clinical trial setting and suggested as a feasible alternative to office BP in primary care.84 87 AOBP refers to a method using fully automated devices capable of recording repeated measurements in short intervals in the absence of medical personnel.88 AOBP correlates well with daytime ABPM or HBPM, thus being superior to conventional office BP by significantly reducing the white-coat effect.89 90 Similar to daytime ABPM and
HBPM, a threshold of 135/85 mmHg should be applied. The routine use of AOBP is already recommended in Canadian Guidelines, and might be considered according to the 2013 ESH/ESC Guidelines on the Management of Arterial Hypertension.

Recommended cut-off values for out-of-office measurements are presented in Table 1-3.

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambulatory BP measurement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>≥ 130</td>
<td>≥ 80</td>
</tr>
<tr>
<td>Daytime</td>
<td>≥ 135</td>
<td>≥ 85</td>
</tr>
<tr>
<td>Nighttime</td>
<td>≥ 120</td>
<td>≥ 70</td>
</tr>
<tr>
<td><strong>Home BP measurement</strong></td>
<td>≥ 135</td>
<td>≥ 85</td>
</tr>
<tr>
<td><strong>Automated office BP</strong></td>
<td>≥ 135</td>
<td>≥ 85</td>
</tr>
</tbody>
</table>

Table 1-3 Classification of out-of-office based blood pressure levels. Adopted from Mancia et al. and Quinn et al.

1.2.3 Treatment of Hypertension

1.2.3.1 Initiation of treatment

Clinical trial evidence obtained between the 1960s and 1990s demonstrated beneficial effects of BP lowering drugs vs. placebo on the major cardiovascular outcomes stroke, myocardial infarction, heart failure and cardiovascular deaths. Long-term treatment for HTN beyond the duration of randomised clinical trials was associated with a more than 50% reduction in cardiovascular disease mortality after 10 years.

With respect to treatment indications, several overall remarks have to be made based on a meta-analyses of 68 randomised controlled trials including 245,888 patients and 1,058,177 patients years of follow-up. Irrespective of HTN grade, pharmacological interventions to lower BP were associated with a significant reduction in all major types of cardiovascular events, including stroke, coronary heart disease, heart failure and cardiovascular death, compared to no treatment, less active treatment or placebo. As demonstrated in Figure 1-2, the benefit is proportional to the decline of systolic BP (SBP) and diastolic BP (DBP) and
particularly pronounced for stroke and heart failure. Since these risk reductions occur in a logarithmic fashion, they increase to a progressively smaller extent the larger the BP reductions are (Figure 1-2).94

Figure 1-2 The association of cardiovascular outcome events and the percentage of blood pressure reduction. Reductions in cardiovascular outcome events are proportional to the reductions of systolic blood pressure, diastolic blood pressure and pulse pressure, without differences between the types of blood pressure. Due to the logarithmic association, risk reduction increases to a progressively smaller extent the larger the blood pressure reduction become. Legend: D-BP: blood pressure difference; CHD: coronary heart disease; HF: heart failure; CV: cardiovascular (Reprinted from Zanchetti et al. with permission of the publisher. Copyright ©2014, Wolters Kluwer Health, license details can be found in the Appendix 94).
The relative and absolute risk reductions achieved for major cardiovascular endpoints are presented Figure 1-3.

Figure 1-3 Relative and absolute risk reduction of cardiovascular outcome events in trials of blood pressure lowering. A, Intentional blood pressure lowering trials. B, Intentional blood pressure lowering trials exclusively in hypertensive patients. C, Intentional and nonintentional blood pressure lowering trials together. Blood pressure lowering significantly reduces the risk for various cardiovascular outcome events, with particularly strong effect for the reduction of stroke and heart failure. Standardised risk ratio (RR) is to a systolic/diastolic blood pressure difference of 10/5 mmHg.

BP lowering was beneficial irrespective of the HTN grade at baseline, or in particular, also in patients with grade 1 HTN. As grade 1 HTN is by far the most prevalent manifestation in a general population, special emphasis should be devoted to this subgroup. In a secondary analysis of patients with grade 1 HTN and low-to-moderate cardiovascular risk (cardiovascular mortality below 5% in 10 years), the authors demonstrated a reduction in major cardiovascular events in favour of active treatment. Also the recent HOPE 3 trial added further hypothesis generating evidence that in patients with HTN grade 1 at intermediate risk without manifest CVD, BP lowering with candesartan plus hydrochlorothiazide might reduce cardiovascular events compared to placebo. There was no benefit for the subgroups in the two lower thirds of baseline SBP, resembling “high normal” BP levels.

Apart from the severity of HTN, recent guidelines suggest the assessment of total cardiovascular risk based on the number of additional risk factors, the presence of organ
damage or the 10-year risk for cardiovascular events. As an inherent consequence of increasing 10-year cardiovascular death incidence (<5%, 5-10%, 10-20%, > 20%), there was a substantially greater absolute risk reduction in higher-risk strata in favour of BP lowering interventions vs. control (Figure 1-4). This implies a greater benefit and consequently a lower number needed to treat for individuals at increasing cardiovascular risk, however, also indicates the higher residual risk in case of treatment failure.94

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**Figure 1-4** Absolute risk reduction by antihypertensive treatment, standardised to a systolic/diastolic blood pressure reduction of 10/5 mmHg, and residual risk for outcome events stratified by cardiovascular risk in the control group. Blood pressure lowering was associated with greater absolute risk reduction in patients at higher baseline risk for cardiovascular events. Also, a higher atherothrombotic risk profile carried a higher residual risk for cardiovascular events when blood pressure lowering fails. Legend: CHD: coronary heart disease; HF: heart failure; HR: high risk; LMR: low-moderate risk; VHR: very high risk; VVHR: very very high risk (Reprinted from Zanchetti et al. with permission of the publisher. Copyright ©2014, Wolters Kluwer Health, license details can be found in the Appendix 94).
Accordingly, the 2013 ESC Guidelines for the Management of Arterial Hypertension recommend pharmacological treatment in individuals with grade 2 and 3 HTN, at any level of cardiovascular risk (class I, level of evidence A). In patients without any additional cardiovascular risk factor or signs of organ damage and grade 1 HTN, pharmacological treatment should be considered when BP remains in an elevated range at several repeated visits or based on out-of-office measurements despite a reasonable period of lifestyle intervention (class IIa, level of evidence B). In patients with grade 1 HTN and additional risk factors or signs of organ damage, a short period of lifestyle changes (several weeks) before initiation of antihypertensive therapy or immediate initiation of antihypertensive therapy are recommended, depending on the number and severity of additional risk factors. Currently, antihypertensive treatment is not recommended in individuals with high-normal BP values at any given cardiovascular risk.

### 1.2.3.2 Treatment targets

Historically, several large-scale trials sought to identify the optimal BP threshold in various sub-groups, particularly diabetes, cerebrovascular disease, high cardiovascular risk and renal disease. In response to these trials, guidelines suggested different treatment goals according to the presence of such co-morbidities. Selected recommendations of current and past guidelines are shown in Table 1-4.

<table>
<thead>
<tr>
<th></th>
<th>General population</th>
<th>Low- to moderate risk</th>
<th>High-risk</th>
<th>Diabetes</th>
<th>Kidney disease</th>
<th>≥ 60 years</th>
<th>≥ 80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESC/ESH 2013</strong></td>
<td>140/90</td>
<td>-</td>
<td>-</td>
<td>140/85</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ESC/ESH 2007</strong></td>
<td>-</td>
<td>&lt; 140/90</td>
<td>&lt; 130/90</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>JNC 7</strong></td>
<td>140/90</td>
<td>-</td>
<td>-</td>
<td>130/80</td>
<td>130/80</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>JNC 8</strong></td>
<td>140/90</td>
<td>-</td>
<td>-</td>
<td>140/90</td>
<td>140/90</td>
<td>150/90</td>
<td>-</td>
</tr>
<tr>
<td><strong>NICE 2011</strong></td>
<td>140/90</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>150/90</td>
</tr>
</tbody>
</table>

Table 1-4 Blood pressure thresholds as recommended by different guidelines
One of the most critically discussed recommendation concerns the optimal BP threshold for patients with high cardiovascular risk. Since the majority (50-70%) of patients in Europe do not achieve HTN control at a threshold of 140/90 mmHg, and because trials lowering BP in high-risk individuals below 140/90 mmHg showed conflicting results, the current guidelines re-appraised the previously recommended BP threshold of <130/80 mmHg in patients with diabetes, cardiovascular- or renal disease. Accordingly, the 2013 ESC Guidelines on the Management of Hypertension recommend a threshold of 140/90 mmHg in all patients (class I, level of evidence B), except for patients with diabetes, in whom DBP values < 85 mmHg are recommended (class I, level of evidence A).

A meta-analysis points towards a further reduction in stroke rates at SBP levels <130 mmHg compared to ≥130 mmHg, without apparent concerns regarding safety. Recently, the SPRINT trial randomised 9361 patients at increased cardiovascular risk but without diabetes to an intensive treatment arm with a SBP target of less than 120 mmHg vs. standard treatment below 140 mmHg. At a median follow-up of 3.3 years, SBP was 121 vs. 136 mmHg in the two treatment arms, which translated into a 57% relative reduction in cardiovascular deaths and a 33% relative reduction of heart failure in favour of intensive treatment. These benefits were counterbalanced by an increase in hypotension, syncope, electrolyte disturbances, and acute kidney failure. An unexpected finding in the SPRINT trial was that the primary endpoint was largely driven by the reduction of heart failure, whereas stroke rates were similar between the treatment groups. Experts therefore hypothesised that the increased use of diuretics in the intensive arm might have unmasked latent heart failure in these elderly patients at increased cardiovascular risk. BP was measured using automated devices in the absence of an observer (AOBP), and obtained values therefore more likely resembled an out-of-office approach. As a result, absolute BP values in the SPRINT cannot be compared to historical trials and potentially resemble office-based values in the range of 140 mmHg for the intensive treatment arm. Since AOBP has been shown to reduce the white-coat effect and to provide values similar to daytime ABPM or HBPM, one has to acknowledge that the superior efficacy achieved in favour of intensive treatment was based on a sound method for BP measurements, potentially supporting the lower SBP threshold (< 130 mmHg).
1.2.3.3 Selection of classes of antihypertensive agents

Extensive data from randomised trials and meta-analyses support the concept that the reduction in cardiovascular outcomes is accounted for by BP lowering per se, irrespective of the drugs used.\textsuperscript{94} Accordingly, ACE-inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs) and diuretics (thiazide diuretics, chlorthalidone, indapamide) are currently recommended as first-line therapy for the initiation and maintenance of antihypertensive treatment.\textsuperscript{83} However, some data point towards heterogeneous findings, and subgroups were identified where the use of specific substance classes might be beneficial.

1.2.3.3.1 Beta-Blockers

Based on trials with moderate or low quality, a meta-analysis concluded that BBs might be inferior to CCBs or inhibitors of the renin-angiotensin-system (RAS) in several hard clinical endpoints, while being similar compared to diuretics, but less well tolerated.\textsuperscript{113} Another meta-analysis found a 16\% increased relative risk of stroke with BBs compared to other antihypertensive agents, whereas compared to placebo, the 19\% reduction in strokes was half of that expected from previous trials.\textsuperscript{114} On the other hand, a meta-analysis of 147 randomised trials including 464,000 patients suggested particularly beneficial effects for BBs given shortly after myocardial infarction and to patients with heart failure.\textsuperscript{115}

1.2.3.3.2 Diuretics

The ALLHAT trial randomly assigned 33,357 patients with HTN and at least one additional coronary heart disease risk factor to either chlorthalidone, amlodipine or lisinopril. After a mean follow-up of 4.9 years, there were no differences in the primary endpoint of fatal coronary heart disease or non-fatal myocardial infarction between groups.\textsuperscript{116} Also, a network meta-analysis of 42 trials concluded that none of the other currently recommended first-line agents (ACEIs, CCBs, ARBs) was superior to low-dose diuretics in any cardiovascular endpoint. Compared with CCBs and ACEIs, the use of low-dose diuretics was associated with a 26\% and 12\% relative reduction in heart failure, respectively.\textsuperscript{117} In contrast, the ACCOMPLISH trial, which randomised 11,506 high-risk patients with HTN to either an ACEI plus amlodipine or an ACEI plus hydrochlorothiazide, demonstrated a reduction in cardiovascular events in favour of the ACEI-amlodipine combination.\textsuperscript{118} Until today, no other randomised trial has shown superiority of a CCB over a diuretic. Based on compelling evidence from previous trials, the data provided by the ACCOMPLISH trial seem to be insufficient to exclude diuretics from first-line treatment.\textsuperscript{83}
1.2.3.3 Calcium Channel Blockers

One of the largest meta-analysis in this setting including 464,000 patients suggested that all first-line classes of antihypertensive agents provide a similar protection against coronary heart disease events and stroke at a given reduction in BP, with the exception of CCBs, which appeared to have a moderate 8% additional risk reduction for strokes. At the same time, new-onset heart failure occurred more frequently using CCBs, which might be a consequence of trials that required the withdrawal of essential therapies in heart failure (ACEIs, BBs, diuretics) in patients assigned to treatment with CCBs. In studies permitting the concomitant use of CCBs and diuretics, BBs or ACEIs, effects on the prevention of heart failure were neutral.

1.2.3.4 Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Compelling evidence generated in the late 1990s demonstrated the beneficial effects of ACEIs and ARBs on various cardiovascular outcomes in hypertensive patients at a high risk for such events. More recently, the ONTARGET trial provided a head-to-head comparison of an ACEI (ramipril) vs. an ARB (telmisartan) vs. a combination of both drugs in 25,611 patients with vascular disease or high-risk diabetes. The occurrence of the primary endpoint, consisting of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure was similar between groups, whereas combination therapy was associated with an excess in adverse events, particularly hypotensive symptoms and renal dysfunction. It is well established, that ACEIs and ARBs provide particular benefits in patients with reduced left ventricular function.

1.2.3.5 Alpha-receptor Blockers

The alpha-receptor blocker doxazosin has been studied in the ALLHAT trial. Compared to a diuretic (chlorthalidone), the use of doxazosin was associated with a significant 25% increase in cardiovascular death, 19% increase in stroke and a doubling in the risk for heart failure. The effects of doxazosin as third-line treatment were investigated in the ASCOT trial. In addition to a mean of 2 other antihypertensive drugs, doxazosin reduced SBP by 12 mmHg, without an apparent excess in heart failure after 12 months of uninterrupted treatment with doxazosin. According to the 2013 ESC Guidelines on the Management of Arterial Hypertension the use of doxazosin should be considered if no contraindications exist (class IIa, level of evidence B).
1.2.3.3.6 Centrally acting agents

Evidence from randomised controlled trials using centrally acting agents such as reserpine or methyldopa is limited to a low number of patients. A meta-analysis of these trials including 1,786 patients, often conducted with background therapy with hydralazine or thiazide suggested significant reductions in stroke, heart failure and cardiovascular death.94

1.2.3.4 Selection of Antihypertensive Drugs – Summary

The 5 major antihypertensive drug classes ACEIs, ARBs, BBs, CCBs and diuretics are recommended for the initiation and maintenance of antihypertensive therapy (class I, level of evidence A). Based on data from randomised controlled trials and meta-analysis, some agents and combinations should be preferred in the presence of specific conditions (Figure 1-5).83 Selected clinical scenarios for which preferred agents have been recommended are presented in Table 1-5.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Substance class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular hypertrophy</td>
<td>ACEI, CCB, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>CCB, ACEI</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>End stage renal disease / proteinuria</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Any agent effectively lowering BP</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>BB, ACEI, ARB</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Diuretic, BB, ACE, ARB, MRA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>ACEI, CCB</td>
</tr>
<tr>
<td>Isolated systolic hypertension in the elderly</td>
<td>Diuretic, CCB</td>
</tr>
</tbody>
</table>

Table 1-5 Preferred antihypertensive substance classes for different clinical conditions. Legend: ACEI: ACE inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, BB: beta blocker, MRA: mineralocorticoid receptor antagonist, BP: blood pressure. Adopted from Mancia et. al.83
Figure 1-5 First-line treatment for hypertension and preferred combinations. Adopted from Mancia et al. \textsuperscript{103}
1.2.3.5 Non-pharmacological treatment options

1.2.3.5.1 Renal sympathetic denervation

Renal sympathetic denervation (RDN) is a percutaneous, catheter-based approach for radiofrequency ablation of renal sympathetic nerves. Evidence regarding potential beneficial effects of sympathectomy on malignant HTN was established in the 1950s.\textsuperscript{127} Patients who were deemed to have malignant or resistant HTN based on markedly elevated DBP values (100-180 mmHg) underwent invasive procedures such as bilateral infradiaphragmatic section of the splanchnic nerves and lumbar sympathetic trunk or even thoracolumbar sympathectomy including supradiaphragmatic resection. The authors observed a marked post-operative decline of DBP followed by a constant increase within days (Figure 1-6).\textsuperscript{127}

![Figure 1-6 Marked decrease in diastolic blood pressure after surgical sympathectomy. Reprinted from Longland et al. with the permission of the publisher, Copyright ©1954 John Wiley and Sons, license details can be found in the Appendix \textsuperscript{127}](image)

In an indirect comparison to medically managed patients with a similar severity of the disease (as determined by fundus grades), there was a survival benefit which was significant at two years of follow-up despite the small sample size of only 46 cases.\textsuperscript{127} In a much larger series of 1,266 surgically and 467 medically treated patients with essential HTN, the authors found a
pronounced survival benefit in favour of thoraco-lumbar splanchnicectomy after up to 10 years of follow-up (Figure 1-7).\textsuperscript{128}

The SIMPLICITY HTN trial program investigated an endovascular catheter-based approach in patients with resistant HTN. The SIMPLICITY HTN-1 open-label, proof-of-concept study enrolled 153 patients with an elevated office SBP ($\geq 160$ mmHg) despite taking $\geq 3$ antihypertensive drug classes, in whom RDN was performed between 2007 and 2010. Baseline office BP was 176/98 mmHg under treatment with an average of 5 antihypertensive drugs. At 12 and 24 months, the investigators observed a highly significant decrease in BP by 23/11 mmHg and 32/14 mmHg, respectively.\textsuperscript{129} These substantial changes in BP, presumably induced by a single procedure, lead to enthusiasm in the cardiovascular field and subsequently called for a randomised comparison against standard of care. Thus, the SIMPLICITY HTN-2 trial enrolled 106 patients with treatment-resistant HTN and randomly allocated patients to
either RDN or optimal medical therapy. At 6 months of follow-up, there was a significant 32/12 mmHg decline of SBP/DPB in patients undergoing RDN, whereas patients in the control group had a non-significant 1/0 mmHg SBP/DBP change compared to baseline. In order to approve RDN for routine use, regulators demanded another randomised trial with a proper control arm using a sham-procedure as comparator.

In the SIMPLICITY-HTN 3 trial, 535 patients underwent randomisation to either RDN or a sham-procedure (renal angiography only) in a single-blinded fashion. In both arms of the trial, there was a significant decline of office SBP (-14 mmHg vs. -12 mmHg) at 6 months, but there was only a non-significant minor between-arm difference of -2.4 mmHg in favour of RDN. Several potential reasons for these negative results have been discussed. One major shortcoming of these trials was that medication adherence was not assessed. The Hawthorne effect, a phenomenon where individuals modify their behaviour (medication adherence) in response to being observed, might have substantially accounted for the decline in BP over time. This is of particular relevance in the setting of resistant HTN, a condition where non-adherence rates lie above 25%. Also, office BP was chosen for the primary efficacy endpoints of these trials, a method which is by far the most unsuitable in a clinical trial setting. Both the white coat effect, as well as the regression of the white coat effect over time might further contribute to the findings of the SIMPLICITY trials. Also, regression to the mean has been discussed to partly explain the substantial BP reduction in the SIMPLICITY trials. Regression to the mean describes a phenomenon of extreme measurements on the first instance being more likely to be closer to the mean when measured on a second instance. The phenomenon is increasingly pronounced with higher baseline values. In contrast to the above mentioned methodological and statistical considerations, demographic and procedural aspects have been shown to have influenced the findings of SIMPLICITY HTN-3. Thus, the SBP reduction in favour of RDN observed in Non-African American patients exceeded the superior margin of 5 mmHg (-6.6 mmHg). Also, patients receiving ≥ 14 ablation attempts had a highly significant -14 mmHg SBP reduction at 6 months.

As elegantly outlined by Gulati et. al., resurrection of RDN is yet to come, perhaps through a reappraisal of trial methodology, patient selection, medication adherence, techniques for BP measurement and procedural aspects. The SPYRAL HTN OFF-MED (NCT02439749) is currently recruiting patients with elevated ABPM who are eligible to discontinue antihypertensive medications. The SPYRAL HTN ON-MED (NCT02439775) will enrol
patients with elevated ABPM employing a strict protocol for the verification of medication adherence (urin sampling). Both trials will use ABPM changes as their primary endpoints. These results are highly anticipated and will set the course for the future of RDN.\textsuperscript{135}

1.2.3.5.2 Baroreceptor stimulation

Baroreceptors are mechanoreceptor sensory neurons, which are located in the carotid sinus, close to the bifurcation of the common carotid artery.\textsuperscript{136} Triggered by pressure-changes in the arterial wall, the innervation occurs through the glossopharyngeal nerve and the nucleus of the solitary tract, modulating sympathetic and parasympathetic activity according to the baroreceptor’s firing rate.\textsuperscript{136} In 1836, Cooper was one of the first to discover the role of baroreceptors in the regulation of BP.\textsuperscript{137,138} In the late 1950s, Carlsten et al. established early evidence in humans by demonstrating that the stimulation of the carotid nerve was associated with a frequency-dependent decrease in BP and heart rate.\textsuperscript{139} The prospective, non-randomised Device-Based Therapy in Hypertension (DEBuT-HT) trial systematically assessed the efficacy and safety of the Rheos implantable device (CVRx, Minneapolis, Minnesota) in patients with resistant HTN.\textsuperscript{140} Between 2004 and 2007, 45 patients with elevated BP (≥ 160/90 mmHg) taking at least 3 antihypertensive drugs were included and followed for 2 years. After 3 months of active device therapy, office SBP was reduced by 21 mmHg, while SBP determined by ABPM was reduced non-significantly by 6 mmHg. At 2 years of follow-up SBP decreased by 33 mmHg (office) and 24 mmHg (ABPM).\textsuperscript{140} The authors concluded that the device was well tolerated and that the BP changes could be attributed to the device rather than to drug treatment, since the intensity of antihypertensive therapy remained unchanged throughout the follow-up.\textsuperscript{140} A patient included into the trial who suffered from malignant HTN with SBP values of up to 240 mmHg despite multi-dug therapy was separately reported. As shown in Figure 1-8, BP and heart rate changed depending on stimulation with the device.\textsuperscript{141}
Following DEBuT-HT, the Rheos Pivotal Trial sought to established superiority over optimal medical therapy in a randomised and double-blind manner. In total, 265 patients were assigned to device implantation and either baroreceptor activation therapy (BAT) for the first 6 months or delayed BAT initiated in the following 6 months. A significant benefit was shown for 3 out of 5 coprimary endpoints (sustained efficacy at 12 months, BAT safety and device safety), while acute response at 6 months and procedural safety did not meet the superiority margin. Using out-patient office BP measurements (BpTRU, VSM Medtech Ltd, Vancouver, Canada) which have been shown to minimize the white-coat effect, the mean decrease in SBP was 16 mmHg vs. 9 mmHg for immediate and deferred BAT (p=0.08). Likewise, the response rate, defined as the proportion of patients with SBP ≤ 140 mmHg was 54 vs. 46%, thus non-significantly different between groups at 6 months (p=0.97). At 12 months, both groups had a statistically similar 25 mmHg reduction in SBP resembling a similarly high response in > 50% of patients.
In the light of the data derived from the RDN trials, the non-significant difference in BP response during the blinded phase of the trial, but marked and sustained reductions in BP in the phase of known treatment assignments generate suspicion about the causal effects of BAT.

More recently, the second generation Barostim neo™ device requiring only one lead was investigated in a single-arm study and found to reduce SBP by 26 mmHg at 6 months.\textsuperscript{143} Two randomised trials are currently investigating the device, the primary completion dates are scheduled for 2018 and 2020, respectively (NCT02364310, NCT02572024).

1.3 Hypertension Control – Available Data in Austria

The only Austrian assessment of HTN control rates mentioned in “The Manual of Hypertension” of the ESH refers to a small, not representative survey of 323 “blue collar” male employees. The prevalence of HTN was 29%, and of those treated 10% had controlled BP.\textsuperscript{144,145}

Two studies reported HTN control rates in primary care in Austria:

The SCREEN II study performed in 2003, including 1303 patients taking at least 30 home BP readings, could show that 17% of treated patients achieved the BP threshold. HTN control was similarly low (16%) in patients attending office-based measurements.\textsuperscript{12}

The more recent but hardly representative international EURIKA study revealed that from 624 patients enrolled in Austria in 2009, 36% achieved the office BP target of < 140/90 mmHg.\textsuperscript{10}

Disease management programs are urgently required to improve BP control and to reduce the burden of the disease.
1.4 Available Data in Europe and the United States

1.4.1 Prevalence of Hypertension

Data from the 80s and 90s consistently indicate a lower prevalence of HTN in the USA (28%) and Canada (27%), opposed to European countries (Sweden 38%, Italy 38%, England 42%, Spain 47%, Germany 55%). The average for North America was 27.6%, compared to 44.2% for Europe. Likewise, average BP values were lower in North America (127/77 mmHg) than in Europe (136/83 mmHg).

Many underlying factors have been considered to explain the cross-Atlantic difference. While the intake of sodium and potassium does not seem to vary to a large extent between the continents, it has been suggested that patterns of alcohol, fruits and vegetable consumption might partly account for the BP differences. Ich bin ein kleines rosa Schweinchen mit Engelsflügeln und trage Stützstrümpfe. The lower BP thresholds throughout the investigated period and their consistency of implementation in North America, resulting in a higher proportion of individuals receiving antihypertensive medication (44%, opposed to 25% - 32% in Europe), could have substantial impact. The results could be biased by a more aggressive approach for screening and treatment of patients with BP below 140/90 mmHg in the United States and Canada (i.e. false-positive reporting).

Genetic factors have also been in the scope of research, however, these attempt seems less plausible since the majority of the North American population is of European ancestry. Additionally, differences in ethnicities were subject to extensive research. It is well established that African-Americans are more likely to suffer from HTN compared to Caucasians and Hispanics. At the same time, African-Americans represent a larger proportion of the population in the USA than in European countries. Hence, the cross-Atlantic gap seems even more pronounced, taking into account that African-Americans alter the prevalence statistics for North American countries in contrast to Europe. Whether the difference in the overall prevalence of HTN between the two continents is rather due to methodological inconsistencies, inherent- or lifestyle factors remains to be fully elucidated.

Gender differences have been discussed controversially: While data from the NHANES indicate a similar prevalence for men and women in the entire period between 1988 and 2008, others suggest that the condition was more prevalent amongst African-American, as well
as white women across regions in America, Africa, Asia and Europe, or even less prevalent among women, as indicated in the Greek EPIC study and representative Canadian surveys. Currently it seems that the prevalence of HTN is higher among men younger than 45, that it is similar between the two genders from 45 to 64 years of age, and in turn higher in women aged 65 or more.

1.4.2 Awareness, Treatment and Control

Data from surveys conducted in the 90s indicate that, based on the current standard of 140/90 mmHg office BP, patients in Sweden, Germany, Spain and Italy were less likely to be treated (25% - 32%) than patients in the United States (53%) or Canada (36%).

Generally, US-Guidelines were more stringent in that period of time, suggesting a threshold of 140/90 mmHg (130/85 mmHg with relevant comorbidities, Joint National Committee IV), whereas Canadian guidelines recommended treatment at 160/100 mmHg for “low-risk” individuals (140/90 mmHg in patients with diabetes or renal disease). The frequently used World Health Organisation / International Society of Hypertension Guidelines in Europe set 150/95 mmHg as cut-off in low-risk patients (130/85 mmHg in patients with diabetes or renal disease). Accordingly, control rates at a level of 140/90 mmHg were higher in US and Canadian population (55%, 47%) compared to European countries, where control rates ranged between 19% (Spain) and 40% (England).

More recent data from the 2004 CardioMonitor survey demonstrate that HTN control at a threshold of 140/90 mmHg was highest in the USA (63%) and substantially lower across Europe (31% - 46%). A medication increase for inadequately controlled HTN was performed in one third of patients in the USA, opposed to 14-26% amongst Europeans. These data also indicate that a significant proportion of cross-national differences can be explained by the lower pre-treatment BP levels in the USA (mean 161/94 mmHg vs. 167-173/96-99 mmHg).

Comparing data obtained from the National Health and Nutrition Examination Survey (NHANES) between 1988-1994 and 2007-2008 including 42,856 individuals, HTN control of treated patients improved from approximately 51% to 69% in the USA. Likewise, the awareness of the disease – assessed by the question “Have you ever been told by a doctor or other healthcare professional that you had hypertension, also called high blood pressure?” – increased from 69% to 81% during that period of time.
Similarly, awareness and HTN control improved from 57% to 83% and 13% to 65% in Canada between 1992 and 2009, respectively, as assessed by the Canadian Heart Health Surveys (CHHS) and the Canadian Health Measures Survey (CHMS) including more than 25,000 individuals.\textsuperscript{153}

Less extensive data are available for Europe, with one of the largest investigations being the Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The latter study included 26,913 volunteers aged between 20-86 years in several regions of Greece. Of those previously diagnosed, 84% were on antihypertensive treatment, however, only 27% had their BP controlled at the level of 140/90 mmHg.\textsuperscript{8} Amongst women, awareness of the condition (60% vs. 46%) and treatment (85% vs. 81%) were higher.\textsuperscript{8}

Accordingly, large-scale studies consistently show that overall treatment and control rates seem to be higher in North America compared to Europe, but still leaving room for improvement on both continents. An overview of HTN control rates in Europe and North America is presented in Figure 1-9.\textsuperscript{58,146}

Since a substantial proportion of data were generated at least a decade ago, further investigations are needed to evaluate the current quality of BP management in a general population.
Figure 1-9  Hypertension control rates in Europe and North America. References: Canada: McAlister et al. 153; USA: Egan et al. 151; France, UK, Spain, Greece, Austria (2010): Banegas et al. 10; Germany: Neuhauser et al. 158; Italy: Tocci et al. 159; Austria (2003): Hitzenberger et al. 12; Bangladesh: Rahman et al. 160
1.5 **Aims of the Thesis**

- To collect data on HTN control in Austria in a large, pre-dominantly adherent cohort
- To assess contemporary treatment patterns in a general population suffering from HTN
- To reduce the shortcomings of previous studies such as bias arising from patient selection or a long data collection period
- To assess awareness for HTN in patients actively obtaining their antihypertensive medication from a pharmacy
- To identify sub-group of patients with particularly poor BP control
- To perform an external validation of treatment effects, rather than “self-evaluation” at clinics or doctors’ practices
- To involve pharmacists into the management of cardiovascular disease
- To establish a basis for future disease management programs
# Results

## 2.1 Prologue

In order to develop well-orchestrated disease management programs, solid data on current BP control rates, treatment patterns, awareness and sub-groups with poor BP control are required.

We sought to perform a study covering these above mentioned aspects while introducing a study design at pharmacies. In contrast to previous studies carried out at outpatients clinics or doctor’s practices the benefit of such a design is that

- treatment effects can be evaluated in an “external” fashion at sites not directly involved in therapeutic decision making, potentially reducing selection bias
- predominantly adherent patients are enrolled, actively approaching pharmacy in order to obtain their antihypertensive medication. This is important because in other study settings, poor control rates can easily be attributed to patients’ non-adherence, disregarding other relevant factors such as physician’s inertia or inadequate treatment. Actively measuring medication adherence, e.g. by electronic pill dispensers or urin-sampling potentially introduces a major bias through the Hawthorne effect. By enrolling patients at pharmacies, we aimed to include a cohort of predominantly adherent patients in an uninfluenced manner.
- pharmacies can be more actively involved in HTN management, with potential long-term effects on the awareness towards the disease on the side of pharmacists and their customers
- in the present study, the collaboration with the Pharmacists College of Lower Austria allowed for a large number of sites to participate

We present the results of our study entitled “Awareness, treatment and control of hypertension in Austria: a multicentre cross-sectional study” and hope that these data will contribute to the understanding and improvement of HTN management in our country.
2.2 PDF of First Paper
Austria: a multicentre cross-sectional study

Awareness, treatment, and control of hypertension in Austria: a multicentre cross-sectional study

Miklos Rohla*a, Heinz Haberfeldb, Maximilian Tscharrea, Kurt Hubera, and Thomas W. Weissa

INTRODUCTION

In the 1990s, child and maternal malnutrition was the leading cause of death worldwide, whereas today hypertension (HTN) is the single largest risk factor for global disease burden, accounting for 9.4 million deaths annually and 7% of disability-adjusted life years [1]. Despite a large variety of effective and well tolerated drugs, HTN control rates, defined as the proportion of treated patients achieving the recommended blood pressure (BP) threshold, have remained on an alarmingly low level for decades in many European countries. The cross-sectional European Study on Cardiovascular Risk Prevention and Management in Daily Practice (EURIKA) study, conducted simultaneously in 12 European countries, could show that only 30% of 7641 treated patients had their BP controlled in 2010 [2].

At the same time, Canada was able to increase BP control from 13% in the 1990s to 65% today, mostly because of the implementation of the Canadian Hypertension Education Program, resulting in a remarkable reduction of myocardial infarctions, strokes, and stroke-related deaths [3,4]. Similarly, low control rates of 17% could be observed in the first large-scale studies conducted in Austria in the late 1990s. Until today no efforts have been made to re-evaluate HTN treatment and control [5,6].

Previous surveys across European countries and North America were mainly conducted at doctors’ offices, clinics, or specialized research centers over a period of months or years, potentially resulting in a biased patient selection and unknown drug adherence, the latter being of particular concern in the management of HTN [2,3,7–9].

Aiming to reduce the above-mentioned shortcomings of the previous surveys, we sought to perform a large-scale cross-sectional assessment of awareness, treatment, and control of HTN in treated patients approaching a pharmacy during a 1-week survey period with a prescription filled for antihypertensive medication.

Background: Hypertension (HTN) control is achieved in 30–50% of all diagnosed and treated patients in Europe today. There is no large, recent, and properly conducted Austrian study available, with the last representative data being obtained in the 1990s. We sought to close this gap of evidence in Europe by providing information on HTN control in predominantly adherent patients.

Methods and results: In October 2015, we enrolled 4303 patients with HTN who approached one of 158 participating pharmacies with a prescription filled for antihypertensive medication. The recruitment was completed within 10 days. Patient’s mean age was 68 ± 12 years, 53% were women. The mean SBP/DBP was 144 ± 20/84 ± 12 mmHg. On average, patients received 2.2 ± 1.1 different antihypertensive substances, 45% received a fixed-dose combination drug. A total of 93% were aware of their disease, 90% claimed to have taken their medication prior to the survey, and 41% had their blood pressure (BP) controlled at a threshold of 140/90 mmHg. Predictors of HTN control were lower age (per decade increase, odds ratio (OR) 0.90, 95% confidence interval (CI) 0.85; 0.96, P < 0.01), female sex (OR 1.23, 95% CI 1.07; 1.41), the intake of medication on the day of the conduct of the survey (OR 2.15, 95% CI 1.67; 2.76), a university degree (OR 1.58, 95% CI 1.19; 2.08), and the consultation of a specialist for internal medicine/cardiology vs. a general practitioner (OR 1.20, 95% CI 1.04; 1.39).

Conclusion: Despite a high degree of awareness and frequent use of fixed-dose combination drugs, only 41% of diagnosed, treated, and adherent HTN patients had their BP controlled. Immediate action is required to improve BP control in Austria.

Video abstract: http://links.lww.com/HJH/A624.

Keywords: adherence, antihypertensive treatment, hypertension control, physician’s inertia

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DMP, disease management programme; FDC, fixed-dose combination drug; HCT, hydrochlorothiazide; HTN, hypertension; MDD, maximum daily dose; MRA, mineralocorticoid receptor antagonists

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METHODS

Study design and participants
The cross-sectional study enrolled patients who were treated for HTN and obtained their antihypertensive medication from a participating pharmacy in the Austrian province of Lower Austria within 10 consecutive working days in October 2015. Patients were included if they were at least 18 years of age and had a prescription filled for antihypertensive medication, that is, for a drug of the following substance classes: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists (MRAs), α-blockers, renin inhibitors, minoxidil, or centrally acting agents such as clonidine, rilmenidine, or moxonidine.

Exclusion criteria were the participation in a clinical study, a first ever prescription of an antihypertensive agent without prior therapy and a prescription not intended for the respective customer.

The Pharmacists College of Lower Austria, a province with a population of 1.6 million, invited all members (239 pharmacies) to participate.

All participating centres underwent an investigator training where the study protocol, inclusion/exclusion criteria, proper seated BP measurement, and data collection were reviewed. In accordance with the 2013 European Society of Cardiology Guidelines on the Management of Arterial Hypertension, pharmacists were instructed to allow patients to sit for 3–5 min before beginning BP measurements, to take at least one measurement on each arm in the sitting position 1–2 min apart, and to take repeated measurements in case of inconsistent values [10]. Participating pharmacists were experienced in the measurement of BP. An oscillometric semiautomatic sphygmomanometer was used at all participating sites (Boso Medicus, Junghening, Germany or Hartmann Tensoval, Wiener Neudorf, Austria).

To minimize selection bias, the enrolment of patients was initially planned for five consecutive working days in October 2015, anticipating an inclusion of four to five individuals per day and per site, thus 1000 patients per day in total.

Using a standardized questionnaire, the following variables were assessed: age, sex, size, weight, marital status, highest completed level of education, employment, inhabitants of the residential area, cardiovascular risk factors, specialty of the prescribing physician, antihypertensive medication, heart rate, and seated BP (at least one reading on each arm).

The awareness of the disease and associated risks were assessed by the question ‘Have you ever been told by a doctor or other healthcare professional that you are suffering from high BP?’ and ‘Have you ever been told that high BP is a risk factor for cardiovascular disease such as stroke and myocardial infarction?’

Additionally, participants were asked whether they were receiving treatment for heart failure and whether they have taken their medication on the day of the conduct of the survey.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee (GS1-EK-4/283-2014 and EK-14-205-VK).

Statistical analysis and outcome measures
Discrete characteristics are expressed as frequency counts and percentages, and differences between groups were determined by the χ² test. Continuous, normally distributed variables are expressed as means with SDs, unless otherwise specified. Differences were examined using the Student’s t test or the Mann–Whitney test, where appropriate. The level of significance used for all tests was a two-sided P value of 0.05.

The BP was calculated as the mean of all available readings and using the reading with the highest systolic value obtained at the individual patient level [10].

In accordance with the 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the Management of Arterial Hypertension, control rates were primarily reported at a threshold of less than 140 mmHg SBP and less than 90 mmHg DBP (mean of available readings) [10].

Additionally, BP control rates are reported at alternative thresholds recommended in currently applicable guidelines [10–12].

A logistic regression model with stepwise backward elimination using a likelihood ratio test with a P level for entry of 0.05 and a P level for removal of 0.2 was applied to analyze predictors of HTN control.

For each substance class and substance, we calculated the total daily dose in proportion to the respective maximum daily dose (MDD), as provided in the prescribing information for the indication ‘arterial HTN’. The applied MDDs are listed in the Supplementary Appendix, Table 1, http://links.lww.com/HJH/A610.

The software package for Social Sciences Version 19 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical calculations.

RESULTS

Study population
From 239 pharmacies in Lower Austria, 158 (66%) pharmacies contributed to the recruitment of patients. Owing to the lower than expected participation at the level of pharmacies, recruitment was extended for five working days after the recruitment of 2938 patients within the first 5 days of the survey period.

Accordingly, 4303 patients were included within 10 consecutive working days in October 2015, reflecting a recruitment of 27.2 ± 14.0 patients per site. The mean age was 68 ± 12 years and 53% of patients were women.

A total of 928 (22%) patients reported to suffer from diabetes, 2058 (48%) reported to have hyperlipidaemia or to receive drug treatment for hyperlipidaemia, and 2010 (47%) patients were current or former smokers. A total of 20% received treatment for heart failure.

General practitioners were responsible for the treatment of HTN in 64% of cases, whereas 30% of patients consulted a specialist for internal medicine or cardiology. Women were
TABLE 1. Sociodemographic data and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Not controlled</th>
<th>Controlled</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 4303</td>
<td>n = 2558</td>
<td>n = 1745</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>68 ± 12</td>
<td>68 ± 12</td>
<td>67 ± 13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>28.55 ± 4.88</td>
<td>28.77 ± 4.89</td>
<td>28.24 ± 4.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (mean, mmHg)</td>
<td>143.92 ± 20.11</td>
<td>155.87 ± 16.34</td>
<td>126.40 ± 9.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP (mean, mmHg)</td>
<td>84.18 ± 11.84</td>
<td>88.99 ± 11.63</td>
<td>77.14 ± 8.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP right arm (mean, mmHg)</td>
<td>143.79 ± 20.88</td>
<td>155.82 ± 17.33</td>
<td>126.15 ± 10.59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP right arm (mean, mmHg)</td>
<td>84.11 ± 12.51</td>
<td>88.91 ± 12.48</td>
<td>77.07 ± 8.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP left arm (mean, mmHg)</td>
<td>144.00 ± 20.66</td>
<td>155.84 ± 17.22</td>
<td>126.64 ± 10.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP left arm (mean, mmHg)</td>
<td>84.24 ± 12.22</td>
<td>89.05 ± 12.03</td>
<td>77.19 ± 8.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (highest, mmHg)</td>
<td>149.09 ± 21.15</td>
<td>161.38 ± 17.47</td>
<td>131.06 ± 10.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP (highest, mmHg)</td>
<td>85.27 ± 12.7</td>
<td>90.03 ± 12.71</td>
<td>78.29 ± 8.88</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (mean, BPM)</td>
<td>71.24 ± 11.56</td>
<td>71.39 ± 12.02</td>
<td>71.01 ± 10.84</td>
<td>0.29</td>
</tr>
<tr>
<td>Heart rate (mean, BPM)</td>
<td>2.47 ± 0.83</td>
<td>2.48 ± 0.84</td>
<td>2.46 ± 0.83</td>
<td>0.52</td>
</tr>
<tr>
<td>Sex</td>
<td>2292</td>
<td>1323</td>
<td>869</td>
<td>0.015</td>
</tr>
<tr>
<td>Marital status Single</td>
<td>319</td>
<td>188</td>
<td>151</td>
<td>0.15</td>
</tr>
<tr>
<td>Married or in a relationship</td>
<td>2817</td>
<td>1663</td>
<td>1145</td>
<td>0.01</td>
</tr>
<tr>
<td>Widowed</td>
<td>816</td>
<td>409</td>
<td>307</td>
<td>0.06</td>
</tr>
<tr>
<td>Not reported/unknown</td>
<td>28</td>
<td>17</td>
<td>11</td>
<td>0.60</td>
</tr>
<tr>
<td>Employment status Employed</td>
<td>753</td>
<td>403</td>
<td>350</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Retired</td>
<td>3249</td>
<td>1986</td>
<td>1263</td>
<td>0.01</td>
</tr>
<tr>
<td>Unemployed</td>
<td>107</td>
<td>60</td>
<td>47</td>
<td>0.27</td>
</tr>
<tr>
<td>Freelancer</td>
<td>166</td>
<td>76</td>
<td>76</td>
<td>0.40</td>
</tr>
<tr>
<td>Highest level of education</td>
<td>1363</td>
<td>846</td>
<td>517</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Compulsory education</td>
<td>1945</td>
<td>1148</td>
<td>797</td>
<td>0.01</td>
</tr>
<tr>
<td>Apprenticeship</td>
<td>599</td>
<td>356</td>
<td>243</td>
<td>0.10</td>
</tr>
<tr>
<td>University degree</td>
<td>327</td>
<td>165</td>
<td>162</td>
<td>0.10</td>
</tr>
<tr>
<td>Not reported/unknown</td>
<td>69</td>
<td>43</td>
<td>26</td>
<td>0.10</td>
</tr>
<tr>
<td>Residential area Major city (&gt;200 000 inhabitants)</td>
<td>155</td>
<td>72</td>
<td>83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>City (20 000–200 000 inhabitants)</td>
<td>768</td>
<td>443</td>
<td>325</td>
<td>0.01</td>
</tr>
<tr>
<td>Town (2000–20 000 inhabitants)</td>
<td>2333</td>
<td>1422</td>
<td>911</td>
<td>0.01</td>
</tr>
<tr>
<td>Village (&lt;2 000 inhabitants)</td>
<td>1046</td>
<td>621</td>
<td>425</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoker</td>
<td>1277</td>
<td>1385</td>
<td>892</td>
<td>0.01</td>
</tr>
<tr>
<td>Former</td>
<td>1421</td>
<td>841</td>
<td>580</td>
<td>0.01</td>
</tr>
<tr>
<td>Current</td>
<td>589</td>
<td>321</td>
<td>268</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>928</td>
<td>598</td>
<td>330</td>
<td>0.01</td>
</tr>
<tr>
<td>Antidiabetic drugs Yes, without insulin</td>
<td>20</td>
<td>14</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Yes, with insulin</td>
<td>681</td>
<td>441</td>
<td>240</td>
<td>0.01</td>
</tr>
<tr>
<td>Not reported/unknown</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td>0.30</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2058</td>
<td>1234</td>
<td>824</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>1740</td>
<td>1026</td>
<td>714</td>
<td>0.01</td>
</tr>
<tr>
<td>ASA</td>
<td>1986</td>
<td>1161</td>
<td>825</td>
<td>0.01</td>
</tr>
<tr>
<td>Awareness 1</td>
<td>1032</td>
<td>581</td>
<td>451</td>
<td>0.01</td>
</tr>
<tr>
<td>Awareness 2</td>
<td>1271</td>
<td>729</td>
<td>542</td>
<td>0.01</td>
</tr>
<tr>
<td>ASA</td>
<td>23</td>
<td>17</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Awareness 1</td>
<td>4003</td>
<td>2412</td>
<td>1591</td>
<td>0.01</td>
</tr>
<tr>
<td>Awareness 2</td>
<td>4058</td>
<td>2405</td>
<td>1653</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Hypertension control in Austria
less likely to suffer from diabetes (19 vs. 25%, *P* < 0.01), to consult a specialist for internal medicine or a cardiology (28 vs. 32%, *P* < 0.01), and they received compulsory education as the highest completed level of education twice as frequently (43 vs. 20%, *P* < 0.01).

Demographic data and clinical characteristics of the study population are presented in Table 1.

**Blood pressure and control rates**

An average of 2.5 ± 0.8 readings was obtained for each patient. All included patients had at least two available readings, and three or more measurements were obtained in 1077 (25%) patients, resulting in a total of 10 631 BP readings.

The mean SBP/DBP of all available readings was 144 ± 20/84 ± 12, the mean heart rate was 71 ± 12 beats/min.

In total, 41% of patients reached the BP threshold of less than 140/90 mmHg, as calculated using the mean of available readings at the patient level, whereas the separate SBP and DBP treatment goal was achieved by 46 and 71% of patients, respectively. HTN grade 1 (≥140/90 mmHg), 2 (≥160/100 mmHg), and 3 (≥180/110 mmHg) were present in 36, 17, and 7%, respectively. Resistant HTN, that is, noncontrolled BP despite the use of three or more different antihypertensive substances, including a diuretic was observed in 18% of the full cohort.

Women had significantly lower SBP, but not DBP values (143.0 ± 20.5/84.4 ± 12.0 vs. 145.0 ± 19.6/84.0 ± 11.7 mmHg, *P* < 0.01/*P* = 0.29) compared with men, and therefore achieved the BP target more frequently (42.2 vs. 38.6%, *P* = 0.02).

BP control was slightly higher in the first vs. the second week of enrolment (41.7 vs. 38%, *P* = 0.02).

In total, 3873 (90%) patients reported to have taken their medication at the day of the survey, thus, before the BP measurement.

Accordingly, we also observed significantly different HTN control rates (42 vs. 29%, *P* < 0.01) and mean SBP/DBP values (149 ± 21/88 ± 13 vs. 143.5 ± 20.8/84 ± 12 mmHg, *P* < 0.01 for both comparisons) depending on medication intake on the day of the conduct of the survey. When excluding patients with resistant HTN and those who did not take their medication before the survey, 51% had their BP controlled.

Control rates at alternative threshold recommended in currently applicable guidelines are presented in Table 2.

### Antihypertensive treatment

All patients received antihypertensive treatment at the time of inclusion into the study, reflecting an average of 1.8 ± 0.9 drugs per patient or 2.2 ± 1.1 different antihypertensive substance classes, when taking fixed-dose combinations (FDCs) into account. General practitioners prescribed 2.1 ± 1.1, whereas specialists for internal medicine or cardiology prescribed 2.4 ± 1.2 antihypertensive substances on average (*P* < 0.01). In total, 32% received antihypertensive monotherapy, 45% of patients received an FDC.

Fixed-dose double combinations with ACEIs/ARBs + hydrochlorothiazide (HCT), ACEIs/ARBs + CCBs, and β-blockers + HCT were used in 30.3, 6.3, and 5.7% of patients, respectively. Fixed-dose triple combinations, that is, ARB + HCT + CCB, were used in 4.5% of patients.
The used dosages of each substance were analysed in relation to the recommended MDDs:

With the exception of rilmenidine, the percentage of the MDD taken was similar between patients who did or did not achieve the BP goal (Table 3). The average percentage of the MDD was 57% for the five most frequently prescribed substances, that is, ACEIs, ARBs, ACEI/ARB + HCT FDCs, \( β \)-blockers, and CCBs, whereas it was the lowest for MRAs (29%).

For loop diuretics, recommended MDDs were higher in indications other than HTN, that is, oedema of cardiac, renal, or hepatic cause. Accordingly, the percentage of the MDD was above 100% as the indication was not accounted for. The antihypertensive treatment is presented in Table 3.

### Awareness

In total, 93 and 95% of patients were aware of their disease, as assessed by the question ‘Have you ever been told by a doctor or other healthcare professional that you are suffering from high BP?’ and ‘Have you ever been told that high BP is a risk factor for cardiovascular disease such as stroke and myocardial infarction?’, respectively.

### Controlled vs. uncontrolled hypertension

As shown in Table 2, we observed significant differences in clinical and sociodemographic characteristics between patients who did or did not achieve the BP threshold of 140/90 mmHg.

Upon multivariable logistic regression modelling, we identified predictors of HTN control, which are presented in Table 4.

Per decade increment in age and per point increment in BMI, there was 10 and 2% relative reduction of HTN control, respectively. The likelihood of achieving the BP target was greater for patients who claimed to have taken their medication prior to the survey (42 vs. 29%, odds ratio (OR) 2.15, 95% confidence interval (CI) 1.67; 2.76, \( P < 0.01 \)), for women (42 vs. 39%, OR 1.23, 95% CI 1.07; 1.41, \( P < 0.01 \)), patients with a university degree vs. compulsory education (50 vs. 38%, OR 1.58, 95% CI 1.19; 2.08, \( P < 0.01 \)), patients who reported to suffer from heart failure (44 vs. 40%, OR 1.35, 95% CI 1.15; 1.58, \( P < 0.01 \)), and patients who consulted a specialist for internal medicine or cardiology vs. a general practitioner (44 vs. 38%, OR 1.20, 95% CI 1.04; 1.39, \( P = 0.01 \)). The significant, stepwise decrease in HTN control by increasing number of clinical risk factors for poor HTN control is shown in Fig. 1. At the same time, a cumulation of traditional cardiovascular risk factors was not associated with HTN control rates (Fig. 2, \( P \) for trend = 0.88).

Upon adjustment, awareness of the disease was associated with lower HTN control rates, since controlled patients were numerically less frequently aware of their disease. The use of FDCs or the number of antihypertensive drugs taken was not associated with BP control upon adjustment.

### TABLE 3. Antihypertensive treatment and percentages of the maximum daily doses per substance class

<table>
<thead>
<tr>
<th>Substance classes</th>
<th>Substance</th>
<th>All patients</th>
<th>Not controlled</th>
<th>Controlled</th>
<th>P value(^a)</th>
<th>P value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACEI</td>
<td>1.79 ± 0.93</td>
<td>2.19 ± 0.11</td>
<td>1.79 ± 0.92</td>
<td>0.52</td>
<td>0.18</td>
</tr>
<tr>
<td>2</td>
<td>ARB</td>
<td>1.45 ± 0.93</td>
<td>2.21 ± 0.11</td>
<td>1.71 ± 0.92</td>
<td>0.38</td>
<td>0.18</td>
</tr>
<tr>
<td>&gt;2</td>
<td>ACEI + HCT</td>
<td>1.45 ± 0.93</td>
<td>2.17 ± 0.10</td>
<td>1.71 ± 0.92</td>
<td>0.52</td>
<td>0.18</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HCT, hydrochlorothiazide; MDD, maximum daily dose; MRA, mineralocorticoid receptor antagonist.

\(^a\)P value for the comparison of antihypertensive drugs between patients who were controlled vs. not controlled.

\(^b\)P value for the comparison of the percentage of MDDs in patients who were controlled vs. not controlled.

For fixed-dose combinations, the percentage of MDDs refers to the ACE inhibitor, angiotensin receptor blocker, \( β \)-blocker or aliskiren.

\( ^{\ast} \)Other refers to fixed-dose combinations, including ramipril + furosemide, spironolactone + furosemide, amiloride + hydrochlorothiazide, triamterene + hydrochlorothiazide, or atenolol + furosemide.
DISCUSSION
The main finding of our study is that despite a high degree of awareness and the frequent use of FDCs, BP was controlled in only 41% of diagnosed and treated patients who actively obtained their antihypertensive medication at a participating pharmacy. When additionally considering the low number of antihypertensive substances used per patient and suboptimal dosing, our data point toward physician’s inertia as the primary cause for poor BP control in our cohort, rather than treatment resistance or nonadherence. Indeed, HTN control was achieved in only 51% when treatment resistance and the lack of medication intake before the BP measurement were excluded.

Until today, the following studies evaluated control rates in Austria.

The SCREEN studies, conducted in the late 1990s, showed that 17% of treated patients had their BP controlled [5,6]. The more recent, but hardly representative analysis of the EURIKA study revealed that from 624 patients enrolled in Austria in 2010, 36% achieved the office BP target [2]. In this study with 7641 patients included in 12 European countries, 39% were controlled, underlining the urgent need for disease management programmes (DMPs) in Europe. As such, the Austrian herz.leben study could achieve a significant 17 mmHg SBP reduction in 2041 patients with uncontrolled HTN and elevated cardiovascular risk through the implementation of a structured DMP.

### TABLE 4. Predictors of hypertension control upon multivariable logistic regression modelling

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade increment)</td>
<td>0.90</td>
<td>0.85 – 0.96</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.98</td>
<td>0.97 – 0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.23</td>
<td>1.07 – 1.41</td>
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CI, confidence interval; OR, odds ratio; Q1, first question.
educational programme [15]. Recently, a randomized evaluation of this educational programme, including 256 patients has been shown to achieve a sustained SBP reduction of approximately 10 mmHg at 6 months vs. a control group not undergoing the structured training [14].

The success of such DMPs can also be witnessed in Germany, where HTN control increased from 23% in 1998 to 51% in 2011 [15].

Through the extensive implementation of the Canadian Hypertension Education Program into primary care, HTN control rates increased from 13% in the 1990s to 65% today, making Canada the world leader in terms of HTN control [3]. This was achieved despite a lower degree of patient’s awareness compared with our cohort, ranging between 80 and 83% in recent surveys [3,7,15]. The dramatic increase of HTN control over time in a similar (Caucasian) patient population compared with Europe and the availability of identical drugs again points toward physician’s inertia as a major cause of poor HTN control in European countries. Accordingly, our data show no differences in the number of antihypertensive drugs between groups at an average of 2.2 antihypertensive substances, indicating a lack of treatment intensification in uncontrolled patients, rather treatment resistance.

We attempted to reduce several shortcomings of previous studies, which were, firstly, the recruitment of participants over a period of months or years, allowing selection bias to occur to an unmeasured extent and, secondly, the unknown adherence to antihypertensive medication which is of particular concern in the management of HTN.

Patients obtained their antihypertensive medication actively and the vast majority claimed to have taken the medication on the day of the conduct of the survey. Expectedly, this was predictive of achieving the BP target [16]. Consistent with previous observations, lower age, lower BMI, and female sex, the absence of diabetes and a high level of education were also associated with BP control [2,17,18].

On the other hand, our study design excluded patients who were not diagnosed, not pharmacologically treated, or intended for treatment by the attending physician, but nonadherent. Therefore, HTN control rates might in fact be lower, as our data are showing the equivalent of ‘on treatment results’ rather than ‘intention-to-treat results’ in clinical trials or a population sample.

**Antihypertensive treatment**

The observed dosing of antihypertensive substances would have allowed up-titration in the majority of cases, particularly in patients who received an MRA. In this setting, the use of FDCs was not predictive of achieving HTN control. This is a strong indicator for an adherent cohort, since a higher likelihood of reaching BP control with FDCs vs. the corresponding free drug combinations can only be observed when adherence patterns vary between the groups [19].

At the same time, the significantly higher number of substances prescribed by specialists for internal medicine or cardiology vs. general practitioners is likely to explain higher control rates in favour of specialists. In fact, the speciality of the treating physician was the only modifiable predictor of HTN control in our analysis, also after adjustment for demographic characteristics and comorbidities. Keeping in mind that a population-based SBP reduction as little as 2 mmHg would be associated with a 10% lower risk of stroke-related deaths, urgent action is required to...
improve BP control in Austria [20]. As a result, DMPs might focus on overcoming physician’s inertia before addressing patient adherence. At an average of 2.2 ± 1.1 antihypertensive substances used in doses largely below the maximum recommended daily doses, the potential for up-titration seems obvious.

Limitations and strengths

There are several limitations to our study. Firstly, we used office BP measurements; thus, the proportion of patients with white-coat HTN or masked HTN was not accounted for. However, to what extent these play a role in the setting of pharmacies has not been investigated previously.

As we only included patients who approached a pharmacy to obtain antihypertensive medication, patients were adherent by definition.

In turn, our data reflect on-treatment rather than intention-to-treat results or a population sample, as mentioned above.

Another strength is the short recruitment period of 10 working days, the data quality and the novel setting at pharmacies.

The external validation of treatment effects at pharmacies might be superior to ‘self-evaluation’ at clinics or doctors’ practices, by further reducing selection bias.

In conclusion, including patients who actively obtained their antihypertensive medication from a participating pharmacy, we demonstrated that despite the frequent use of FDCs and a high degree of awareness, only 41% of diagnosed, treated, and predominantly adherent patients achieved the BP goal.

When also considering the low number of antihypertensive substances used and their insufficient dosing, our data point toward physician’s inertia as the primary cause of poor BP control in our representative cohort, rather than nonadherence.

These alarming results might encourage healthcare providers to implement DMPs into primary care.

ACKNOWLEDGEMENTS

We would like to acknowledge Jan Pazourek from the Health Insurance Fund of Lower Austria, and all participating pharmacists of Lower Austria, who willingly agreed to support our research.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

Reviewers’ Summary Evaluations

Reviewer 2
The authors describe a study which has been carried out in pharmacies. This makes it clear why there are no details provided with regard to blood pressure recording such as dominant or non-dominant arm, speed of deflation etc. and we have a lack of information how many individuals were invited and did not participate in the study. There is also not a good control of drug intake. However, this study is unique in the design and reporting the information in Austria which can be expanded to Middle Europe.

Reviewer 3
A ‘quick and dirty’ approach to have some information on patient compliance to antihypertensive therapy. Nice because it may be repeated at intervals without being extremely resource demanding, since many pharmacies can work together and over a short period accumulate a large patient number. The down side is that many non-compliant patients may not even show up at the pharmacy, and thus the compliance problem may be grossly underestimated.

This is NOT a population sample. Since compliance even under these circumstances came out problematic, the real problem in Austria is undoubtedly much larger than reported. A result calling for action.
3 Discussion

3.1 General Discussion

We sought to assess the awareness for HTN, treatment patterns and BP control in a general Austrian population using a novel study design at pharmacies. The study could show that amongst 4.303 patients suffering from HTN and approaching a pharmacy in order to obtain their antihypertensive medication, only 41% had their BP controlled. Also when excluding patients who reported not to have taken their medication prior to the survey and who were treatment resistant per definition (receiving three or more different antihypertensive drugs including a diuretic), only 51% were found to have controlled BP.

These results have to be interpreted considering previous data available from Austria and also in a global context. The following two studies investigated HTN control rates in Austria:

Conducted in the late 1990s, the SCREEN II study included 1.303 HTN patients treated by 166 different (mostly) resident physicians. In total, 39,000 home BP readings were obtained (at least 30 per patient). The currently used threshold of 135/85 mmHg was applied to categorise patients into normotensive vs. mildly or severely hypertensive. As recommended by an Austrian consensus statement, the presence of at least 7 elevated readings was considered diagnostic of HTN. The authors reported that despite an established diagnosis, medical treatment and availability of a home BP monitor, only 17% of patients had their BP controlled.

In 2009, the multi-national EURIKA study included 7641 patients at least 50 years of age, free of clinical cardiovascular disease but with at least one cardiovascular risk factor, and assessed the achievement of treatment goals in Europe. A total of 809 participating physicians were identified from a database for practicing physicians, the majority of them (64%) being general practitioners. On-site data monitoring was performed for 10% of study centres in a random fashion. The prevalence of HTN was 73%, and 94% were drug treated. Across 12 European countries, HTN control was achieved in 39% of patients when applying a threshold of 140/90 mmHg. Only 447 HTN patients enrolled in Austria were available for analysis, of whom 36% had their BP controlled.
By using a novel study design, we sought to address some shortcomings of these previous studies. Firstly, our data represent an “external” validation of treatment effects independent of the site of treatment, potentially reducing selection bias. The short recruitment period might have contributed to reduce selection bias. Also, most previous studies did not attempt to assess the adherence to antihypertensive medication, which is of particular concern in the management of HTN. In a clinical trial database of 4.783 patients treated for HTN, every second patient has been found to discontinue treatment at one year of follow-up, as assessed by dosing histories of electronic pill dispensers. In patients with apparent treatment resistant HTN, urine mass spectrometry testing revealed that 25% were partially or totally non-adherent to antihypertensive therapy.

As we included patients on pre-existing antihypertensive drug therapy who actively approached a pharmacy in order to obtain their medication we assumed participants to be predominantly adherent. Participants were specifically queried regarding compliance to medication on the day of the conduct of the survey. Ten per cent claimed not to have taken their medication on the day of study participation, which was a strong predictor for HTN control. Accordingly, the study seems to have properly identified a diagnosed, treated and adherent cohort of patients with HTN.

In a European context, HTN control rates are in the range of neighbouring countries of Austria. Data from two German national health survey reported that HTN control increased from 23 to 51% between 1998 and 2008-2011. A large-scale Italian survey including 158.876 patients between 2005 and 2011 reported that 37% of treated participants achieved controlled BP levels. Recently, HTN control rates have been reported from the Bangladesh Demographic and Health Survey, including 7.876 adults from all income classes. Overall, 32% had their BP controlled, which is higher compared to data from several industrialised countries.

Through the implementation of the Canadian Hypertension Education Program (CHEP), Canada was able to increase BP control rates from 13% in the 1990s to 65% in 2009 and therefore represents the leading country in terms of HTN control. The improvement in HTN control was timely linked to a marked decline of HTN-related cardiovascular disease such as stroke, heart failure and myocardial infarction, starting from 1999. Whilst the reduction in myocardial infarction related mortality can also be attributed to improved antithrombotic strategies and the emerging field of percutaneous coronary interventions, the
reduction in hospitalisation rates for stroke and deaths from stroke seemed to be tightly associated with an increase in antihypertensive prescriptions.\textsuperscript{164} Similar results were obtained by the National Institute of Health Examination Survey (USA). Between 1988-1994 and 1999-2008 the survey included 42,856 adults representing a probability sample of the US population. BP control increased from 27% in 1988-1994 to 50% in 2007-2008 across all age groups, ethnicities and genders, largely owing to improvements in awareness and adequate antihypertensive treatment.\textsuperscript{151} These results might be biased by the limited accessibility to the healthcare system, potentially overestimating HTN control rates for a general population in the US.\textsuperscript{165} The marked increase in HTN control in the Canadian and US population in a predominantly similar (Caucasian) patient population compared to Europe points towards physician’s inertia as a major contributor to poor BP control.\textsuperscript{151,153} Due to the design of our study we were unable to include patients who were not diagnosed, not pharmacologically treated or non-adherent to medical treatment. Accordingly, population-based HTN control rates in Austria are most likely to be lower than suggested by our results when keeping in mind that cohorts with a lower likelihood for adequate BP control were excluded from our study.

### 3.1.1 Antihypertensive Therapy

On average, patients in our study received 2.2 different antihypertensive substances or 1.8 antihypertensive drugs, when taking fixed-dose combinations into account. The average percentage of the maximally allowed daily dose for the five most frequently prescribed substance classes (ACEI, ARBs, ACEI/ARB + HCT, BBs and CCBs) was 57%. Accordingly, therapy intensification, either by adding another drug or by up-titration of pre-existing therapy could have been easily achieved in the majority of patients.\textsuperscript{161} Upon multivariable adjustment, the use of fixed-dose combination drugs was not associated with HTN control. This indicated that the enrolled cohort was indeed predominantly adherent to therapy, since differences in the effectiveness of fixed-dose combinations versus the free-drug components could only be observed if also a difference in adherence was present.\textsuperscript{161,166}
3.1.2 Predictors of Hypertension Control

Upon multivariate analysis we identified several factors associated with BP control.\textsuperscript{161}

As also shown by others, the likelihood for achieving BP was inversely associated with age.\textsuperscript{167} BP, arterial stiffness and pulse pressure increase with age and at the same time, antihypertensive therapy might not be intensified accordingly because normotensive BP values are less well tolerated in the elderly and are more difficult to achieve.\textsuperscript{167,169} The Eight Joint National Committee Guidelines issued in 2014 increased the recommended SBP target from 140 to 150 mmHg for patients aged 60 or above.\textsuperscript{106} These recommendations raised major concerns amongst experts since some argue that there is insufficient evidence to clearly support the higher BP target and it might prompt physicians to reduce the intensity of antihypertensive therapy in a large population at risk for cardiovascular events.\textsuperscript{170-172} In response to these recommendations, a post-hoc analysis of the INVEST trial, randomising patients with HTN and coronary artery disease to either atenolol/hydrochlorothiazide vs. verapamil/trandolapril was published. In a propensity-score adjusted model, the risk of cardiovascular mortality and stroke increased by 34\% and 89\% in patients who achieved a SBP of 140 to 150 mmHg vs. <140 mmHg, respectively.\textsuperscript{173} The authors therefore concluded that the recommendations by the Eight Joint National Committee Panel might be associated with less benefits for patients aged 60 years or above compared to the previous treatment target of 140 mmHg.\textsuperscript{173} A recent meta-analysis of 21 randomised trials found high-strength evidence that lowering BP to less than 150/90 mmHg in adults ≥60 years of age reduces stroke risk by 26\%, cardiac events by 23\% and mortality. Low- to moderate strength evidence suggested that lowering the target BP to 140/85 mmHg was associated with a 21\% relative risk reduction in stroke rates at the cost of an increase in medication burden, syncope and hypotension but not in quality of life, falls or cognitive impairment.\textsuperscript{174} Accordingly, lowering SBP below 140 mmHg in patients aged 60 years or above, as recommended by other current guidelines, most likely reduces the risk of cerebrovascular events, particularly in patients with a prior stroke.\textsuperscript{83,172,174} The trade-off between efficacy and potential harms might prompt for an individualised approach in many patients.

In patients who reported to suffer from heart failure in our study, the more frequent use of diuretics or MRAs, the natural course of the condition and perhaps more frequent visits at specialists could account for lower BP values in this population.\textsuperscript{161} Generally, specialists for internal medicine or cardiology prescribed a significantly higher number of antihypertensive
substances (2.4 vs. 2.1, p<0.01), which could explain the higher rate of HTN control achieved by specialists.161

As mentioned before, 10% claimed not to have taken their antihypertensive medication at the day of the conduct of the survey, which expectedly resulted in higher BP levels in these patients. Women and participants with a higher level of education were more likely to have their BP controlled, whereas patients with diabetes had a 20% lower likelihood of achieving the BP threshold.161 Differences in awareness, healthcare utilisation and age-dependent endocrine changes have been discussed to explain the disparity in BP control between men and women.154 175 176

We identified a cluster of 5 clinical risk factors for poor BP control, including age ≥ 65 years, male gender, presence of diabetes, compulsory education and non-treatment by a specialist for internal medicine or cardiology. While the number of traditional cardiovascular risk factors (hyperlipidaemia, smoking, family history for cardiovascular disease and diabetes) was not significantly associated with BP control, there was a step-wise and significant decrease in BP control rates along with an increasing number of clinical risk factors.161 BP was controlled in 55% of patients in the absence of a clinical risk factors, compared to 30% in those with all five risk factors present.161 This underlines that special emphasis should be devoted certain subgroups of patients with particularly poor HTN control and high cardiovascular risk without disregarding the overwhelming majority of the population with easy-to-treat HTN.
3.1.3 Strengths and Limitations

The strengths of our study include a short recruitment period and a large number of enrolling centres, potentially reducing selection bias. Also, the external validation of antihypertensive treatment and BP control rates at pharmacies might further reduce selection bias. Prior studies were mainly carried out at clinics or doctor’s practices, i.e. at a site directly responsible for therapeutic decisions.\textsuperscript{10,12}

Shortcomings of our study are that BP was measured in a setting resembling an office-approach. ABPM or home BP readings were not available, hence, white-coat HTN and masked HTN could not be accounted for. To which extent these two phenomena affect BP read-outs at pharmacies is unknown. As previously mentioned, enrolled patients actively approached a participating pharmacy in order to obtain their antihypertensive medication. Due to the enrolment of a predominantly adherent cohort, we were unable to assess HTN control rates on a population basis, taking non-adherent or not pharmacologically treated patients into account. Our results might only generalisable to other regions of Austria with a certain margin of fluctuation.\textsuperscript{161}

3.1.4 Conclusion

In October 2015, we were able to enrol a large cohort of patients suffering from HTN, who actively obtained their antihypertensive treatment from a participating pharmacy. In this predominantly adherent cohort, we could demonstrate that despite a high degree of awareness and the frequent use of modern fixed-dose combination drugs only 41\% had their BP controlled. Given the number of antihypertensive drugs used and their dosing, up-titration of therapy could have been easily achieved in the majority of patients. We therefore hypothesise, that physician’s inertia is a major contributor to poor HTN control in our cohort. These results might prompt healthcare providers to implement specifically designed disease management programs into primary care.\textsuperscript{161}
3.1.5 Future Prospects – What Can Be Done to Improve Blood Pressure Control

As demonstrated in the CHEP, healthcare interventions can result in substantial improvements of both, surrogate parameters (BP control) and hard clinical endpoints (HTN related cardiovascular events) within a reasonable period of time. The CHEP provides easily accessible, simple and concise resources for professionals and patients (www.guidelines.hypertension.ca). However, in most parts of the world such dedicated disease management programs do not exist, and most national and international guidelines are overly complex. Quantitatively, HTN management takes place in primary care, where physicians often do not have the resources and training to treat the majority of their patients to target. Frequently, specialists for internal medicine are only involved with the treatment of HTN in the setting of secondary prevention, i.e. when an undesirable outcome event has already occurred. A group of international experts identified major barriers for the improvement of HTN control in Europe and suggested five key actions:

- identify the BP target of less than 140/90 mmHg for the majority of patients,
- simplify treatment strategies (encourage pill reduction),
- address therapeutic inertia,
- improve patient empowerment and
- involve healthcare providers

![Figure 3-1: Key actions to improve blood pressure control identified by a group of international experts.](image)

Legend: HT: hypertension; BP: blood pressure. Reprinted from Redon et al. with permission of the publisher. Copyright ©2016, Wolters Kluwer Health, license details can be found in the Appendix.
In the authors opinion, it should be one of the main concerns of HTN experts in Austria to actively convey this information to healthcare providers and primary care physicians.

One of our research group’s focus is to involve pharmacists into the management of HTN.

The randomised RxEACH study could recently demonstrate that an intervention by community pharmacists vs. usual care was associated with a reduction in CVD risk through improvements in low-density lipoprotein cholesterol, SBP, glycosylated haemoglobin and smoking cessation.\textsuperscript{178}

Based on the data derived from the presented cross sectional study \textsuperscript{161}, we plan to perform a cluster-randomised trial allocating pharmacies to an observational arm and an interventional arm. In the interventional arm, pharmacists will identify patients with inadequately treated HTN using AOBP devices and refer them to the treating physician for therapy intensification. We hope that through this trial, we can implement a feasible strategy to improve BP control involving pharmacists and primary care physicians.
4 Methods & Materials

4.1 Methods

4.1.1 Study Design

The study was designed as a large-scale, multicentre, cross-sectional assessment of awareness, treatment and control of HTN in Lower Austria.

In total, 238 pharmacies were potentially available for patient recruitment.

All participating investigators were invited for an investigator training where the study protocol, applicable aspects of the Good Clinical Practice guidelines, inclusion/exclusion criteria, consent for participants, proper BP measurement and data collection were reviewed. These details of the study protocol are discussed below in detail. During the recruitment period, details for the proper conduct of the study were also made available online.

The aim of the study was to include a broad sample of patients who were treated for HTN and approaching a pharmacy in order to obtain their antihypertensive medication. Thus, the study was carried out using a novel study design in order to reduce the shortcomings of previous cross-sectional assessments of HTN control. These were

- the inclusion of patients during a period of months or years, potentially resulting in a biased patient selection,
- the enrolment of patients at doctor’s offices, clinics or specialised research centres which might lead to “internal” rather than “external” validation of the treatment effects and
- the unknown drug adherence, being of particular concern in the setting of HTN.
4.1.2 Inclusion / Exclusion Criteria

4.1.2.1 Inclusion criteria for pharmacies

An automated, oscillometric BP device must be available at all participating pharmacies

4.1.2.2 Inclusion criteria for patients

- Prescription for an antihypertensive drug, as defined in 4.1.3
- Age > 18 years

4.1.2.3 Exclusion criteria for patients

- Participation in a clinical study
- First ever prescription of an antihypertensive agent without prior therapy
- Prescription not intended for the respective customer

4.1.3 SOP’s – Patient Recruitment

Standard operating procedures (SOPs) for patient recruitment were defined in the study protocol and trained during the investigators meetings.

Investigators were encouraged not to perform patient selection based on personal estimation regarding compliance/adherence or the potential usefulness of participation for the individual customer/patient. Also, investigators were particularly advised to maintain a consecutive patient recruitment throughout the study period. Per site, 15 to 25 patients should be included to minimise over/under representation of sites or regions.

The enrolment of participants was initially scheduled for five consecutive working days in October 2015, anticipating an inclusion of 4-5 patients per site, hence, 1000 patients per day in total.

In order to qualify patients as being treated for HTN, the following substance classes were regarded as antihypertensive treatment:
• ACEI, ARBs
• BBs
• CCBs
• Diuretics (Loop diuretics, thiazided)
• MRAs (spironolactone, eplerenone)
• Alpha Blockers
• $\alpha_2$-Agonists (such as clonidine, methyldopa, moxonidine)
• Renin-Inhibitors (aliskeren)
• Direct vasodilators (such as minoxidil, hydralazine)

4.1.4 SOP’s – Blood Pressure Measurement

All pharmacists were experienced in the use of automated, oscillometric devices. Devices from Boso Medicus® (Jungingen, Germany) and Hartmann Tensoval® (Wiener Neudorf, Austria) were used in the study. To ensure inter- and intra-observer consistency, a proper BP measurement technique in accordance with the 2013 ESC Guidelines on the Management of Arterial Hypertension was reviewed during the investigator meetings. Standard operating procedures were made available online for all investigators.83

The following specific recommendations were issued:

• Investigators should allow patients to sit for 3-5 minutes before beginning BP measurements
• At least two measurements should be obtained, in the sitting position, 1-2 minutes apart.
• BP measurements should be performed on both arms
• A standard bladder (12-13 cm wide und 35 cm long) should be used, but a smaller or larger bladder should be available if needed.
• The cuff should be at the heart level, irrespective of the position of the patient
• An automated, oscillometric device should be used (inclusion criterion for pharmacies)
• In case of varying BP values upon the first measurements, repeated measurement should be taken and documented
4.1.5 Endpoints

4.1.5.1 Primary Endpoint

The pre-defined primary endpoint was the proportion of patients achieving BP control at a threshold of < 140/90 mmHg (mean of all available readings). As co-primary endpoints, BP control rates were also reported according to currently applicable guidelines (ESH/ESC, NICE, Eight Joint National Committee).83 106 107

4.1.5.2 Secondary Endpoints

As secondary endpoint, factors associated with HTN control were analysed using a multivariate logistic regression model, account for the following potential confounders

- Age
- Gender
- Body mass index
- Presence of diabetes
- Tobacco use
- Heart failure
- Highest level of education
- Residential area
- Marital status
- Awareness
- Prescribing physician’s specialty
- Number of antihypertensive drugs taken
- Use of fixed-dose combination drugs
- Medication intake prior to the survey
4.1.6 Statistical Consideration

4.1.6.1 Sample-Size Calculation

In order to reflect an ample proportion of subjects treated for HTN in Austria, up to 238 pharmacies were designated to enrol 15-25 patients per site (4-5 patients per site per day) within 5 consecutive working days, resulting in an anticipated maximum sample size of 5000. In case of lower than expected participation at the level of pharmacies or patients an optional extension to a total of 10 consecutive working days was pre-scheduled.

4.1.6.2 Methods for Preventing Bias

In order to minimise detection bias, all investigators were required to be equally trained and experienced in BP measurements and utilization of automated devices. Selection bias on patient level might occur, as more compliant/adherent patients are empirically more likely to participate in studies. However, owing to the study design, the majority of patients were anticipated to be adherent since they actively obtained their antihypertensive medication of the respective pharmacy. The duration of enrolment was scheduled for 5 consecutive working days (with optional extension to 10 consecutive working days) to further minimise selection bias. The “external” validation of treatment effects might also be superior regarding selection bias compared to the “internal” validation at doctor’s practices or outpatient clinics.

4.1.7 Risks Associated with the Study Participation

These cross-sectional study was not expected to carry any risks for participants. BP measurements were performed non-invasively and by trained personnel to ensure proper handling. Through the attention drawn towards HTN, beneficial long-term effects could be expected for individuals unaware of their BP.


4.1.8 Gender Aspects

In large-scale studies, conflicting data with respect to the overall prevalence of HTN according to gender have been reported. Differences have been found between age groups, thus, the prevalence of HTN was higher among men younger than 45, the prevalence was similar between the two genders form 45 to 64 years of age, and above 65 women were more likely to suffer from HTN.

Since no gender-specific exclusion criteria have to be met (breastfeeding, women of childbearing potential), both genders are expected to be equally represented in the study.
## 4.2 Materials

### 4.2.1 Case Report Form

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<td>Leiden Sie an Diabetes (Zuckerkrankheit)?</td>
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<td>Haben Sie erhöhte Cholesterinwerte oder nehmen Sie Cholesterinsenker (sog. Statine)?</td>
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<td>Stehen Sie wegen Herzschwäche unter Behandlung?</td>
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<td>Haben Sie Familienmitglieder die einen Herzinfarkt oder Schlaganfall erlitten haben?</td>
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<td>Lipidenker (Statine oder andere)</td>
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<td>Antidiabetika (oral oder parenteral)</td>
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<td></td>
<td></td>
<td>Ja, ohne Insulintherapie</td>
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## Antihypertensiva

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<td><strong>ATII Antagonisten (Sartane)</strong></td>
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<tr>
<td>Kombipräparat:</td>
<td>ACEI oder ATII Blocker + Amlodipin</td>
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<td>ATII Blocker + Amlodipin + HCT</td>
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<td>(zB Doxazosin)</td>
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## Gesamte orale Dauermedikation

### Anzahl aller PRÄPARATE (gesamte orale Dauermedikation inkl. Antihypertensiva)

- 

### Anzahl aller TABLETTEN (Stückzahl, gesamte orale Dauermedikation inkl. Antihypertensiva)

- 

60
5 References


90. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. *J Hypertens* 2009;27(2):280-6. doi: 10.1097/HJH.0b013e32831b9e6b


109. Kjeldsen SE, Narkiewicz K, Hedner T, et al. The SPRINT study: Outcome may be driven by difference in diuretic treatment demasking heart failure and study design may support systolic blood pressure target below 140 mmHg rather than below 120 mmHg. *Blood Press* 2016;25(2):63-6. doi: 10.3109/08037051.2015.1130775


6 Appendix

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Publication: Journal of Hypertension

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Since 10/2016

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Residency
07/2016 – 09/2016

Wilhelminenhospital, Vienna, Austria
Department of Vascular Surgery
Residency
04/2016 – 06/2016

Wilhelminenhospital, Vienna, Austria
5th Medical Department, Endocrinology and Rheumatology
Residency
01/2016 – 03/2016
Wilhelminenhospital, Vienna, Austria
3rd Medical Department, Cardiology and Intensive Care Medicine
Clinical Research Coordinator and Employment for Thesis Elaboration 09/2012 – 12/2015

Medical University of Vienna, Institute of Anatomy, Vienna, Austria
Supervising Tutor for the Neuroanatomy and General Anatomy Dissection Course 2012 – 2013

Professional Interests

♦ Atrial Fibrillation (antithrombotic therapy, anticoagulation, patient management)

♦ Coronary Heart Disease (antithrombotic therapy, invasive revascularization, patient management)

♦ Invasive Sub-Specialities (transcatheter coronary interventions, invasive rhythmology, device therapy)

♦ Hypertension (clinical and invasive, including percutaneous renal denervation)

Publications (only peer-reviewed and Pubmed-listed)


Platelet turnover predicts outcome after coronary intervention.

Epicardial adipose tissue and cardiovascular outcome in patients with acute coronary syndrome undergoing percutaneous coronary intervention.
Eur Heart J Acute Cardiovasc Care. 2016 Nov 18 [epub ahead of print]
   Impact of Bivalirudin on Mortality and Bleeding Complications in Acute Coronary Syndrome Patients Undergoing Invasive Revascularization - A Real-world Experience

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*Metabolic syndrome, inflammation and atherothrombosis.*
Clinical Trial Experience

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<td>08/2012 – 12/2014</td>
</tr>
<tr>
<td>ISAR SAFE</td>
<td>10/2012 – 02/2014</td>
</tr>
<tr>
<td>ATLANTIC</td>
<td>10/2012 – 11/2013</td>
</tr>
<tr>
<td>RIVER PCI</td>
<td>06/2012 – 09/2013</td>
</tr>
<tr>
<td>TAO</td>
<td>10/2012 – 03/2013</td>
</tr>
<tr>
<td>RELY-ABLE</td>
<td>10/2012 – 03/2013</td>
</tr>
<tr>
<td>ACCOAST</td>
<td>06/2012 – 01/2013</td>
</tr>
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Awards

2014 – Werner Klein Grant – Austrian Society of Hypertension (€ 10.000.-)  
“Lowering Blood Pressure in Primary Care in Vienna”

2014 - Academic Excellence Scholarship of the Medical University of Vienna

2014 – Best Abstract Award of the Austrian Society of Cardiology  
“Long-term clinical outcomes of patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation for acute and stable coronary artery disease”

2013 - Academic Excellence Scholarship of the Medical University of Vienna

2012 - Academic Excellence Scholarship of the Medical University of Vienna

Languages

German (fluent in written and spoken)  
Hungarian (fluent in written and spoken)  
English (fluent in written and spoken)

Vienna, March 2017            Miklos Rohla