Blood Pressure-Lowering Therapy

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Abstract

Extensive evidence demonstrates that lowering blood pressure can substantially reduce the risk of atherosclerotic cardiovascular disease and death.

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In light of the latest 2018 European Society of Cardiology/European Society of Hypertension Joint Guidelines, we summarize the current recommendations about lifestyle intervention strategies, pharmacotherapy, and device-based treatments for the management of arterial hypertension. Special attention is given to direct effects exerted by some antihypertensive drugs targeting vascular wall cell components that are involved in the pathogenesis of atherosclerosis.

**Keywords**

Blood pressure medical treatment · Cardiovascular risk factors · Device therapy · Hypertension · Hypertension-driven atherosclerotic complications · Lifestyle interventions

**Abbreviations**

ACE Angiotensin-converting enzyme  
Ang II Angiotensin II  
ARBs Angiotensin II receptor blockers  
BP Blood pressure  
CCBs Calcium channel blockers  
CVD Cardiovascular disease  
ESC European Society of Cardiology  
ESH European Society of Hypertension  
MR Mineralocorticoid receptor  
NO Nitric oxide  
ROS Reactive oxygen species  
SHF Swiss Heart Foundation  
SNSF Swiss National Science Foundation

**1 Introduction**

Continuous progress in understanding the epidemiology, pathophysiology, and pharmacology of arterial hypertension has consistently improved the possibility of an efficient and safe treatment of elevated blood pressure (BP).

Extensive evidence demonstrates that lowering BP can substantially reduce the risk of cardiovascular disease (CVD) and death with similar proportional reductions across various population subgroups. Every 10 mmHg systolic BP reduction significantly diminished the risk of major CVD events (RR 0.80, 95% CI 0.77–0.83), coronary heart disease (0.83, 0.78–0.88), stroke (0.73, 0.68–0.77), heart failure (0.72, 0.67–0.78), and all-cause mortality (0.87, 0.84–0.91) (Ettehad et al. 2016).

Arterial hypertension is characterized by structural and functional changes in blood vessels, which lead to increased arterial stiffness, vascular inflammation, endothelial dysfunction, fatty streaks, early atherosclerotic plaque, plaque progression, and plaque rapture. Vice versa, arterial stiffness, endothelial dysfunction, and
vascular inflammation may also contribute to increased BP. Several lifestyle interventions and drugs lowering BP were demonstrated to improve endothelial function, decrease arterial stiffness and vascular inflammation, and ultimately prevent the development and/or progression of atherothrombosis. After exclusion of the main causes of a secondary hypertension, lifestyle modifications should be suggested as BP and cardiovascular risk lowering strategy to every patient with arterial hypertension. However, sooner or later, most patients diagnosed with arterial hypertension will require a pharmacological therapy. According to the 2018 ESC/ESH Guidelines (Williams et al. 2018), the necessity of a pharmacological therapy will be defined by the grade of arterial hypertension (see Table 1), the cardiovascular risk, and the presence of hypertension-mediated organ damage or concomitant diseases such as a history of cardiovascular events, diabetes mellitus, or chronic kidney disease. The 2018 Guidelines suggest as general rule to reduce office BP below 140/90 mmHg aiming to reach a BP around 130/80 mmHg; see Table 1. The ultimate goal of antihypertensive therapy is the prevention of cardiovascular events. The higher the absolute cardiovascular risk, the more likely it is that a patient will benefit from a more aggressive BP goal. However, although cardiovascular events generally decrease with more intensive lowering of BP, the risk of adverse effects, cost, and patient inconvenience increase as more medication is added (Ettehad et al. 2016; Williams et al. 2018). See Fig. 1. This recommendation together with good clinical judgment and shared decision-making between patients and care providers should guide our BP-lowering therapy.

### Table 1
From ESC/ESH guidelines for hypertension, Eur Heart Journal 2018 (©ESC/ESH 2018)

| Category | Systolic (mmHg) | Diastolic (mmHg) |
|----------|----------------|-----------------|
| Optimal  | <120           | <80             |
| Normal   | 120–129        | 80–84           |
| High normal | 130–139      | 85–89           |
| Grade 1 hypertension | 140–159 | 90–99         |
| Grade 2 hypertension | 160–170 | 100–109        |
| Grade 3 hypertension | ≥180   | ≥110           |
| Isolated systolic hypertension | ≥140   | <90            |

**BP** blood pressure, **SBP** systolic blood pressure
The same classification is used for all ages from 16 years

*BP* category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic

Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

#### 2 Non-pharmacological Therapy

Treatment of hypertension should always include non-pharmacological therapy (Fig. 1) (Williams et al. 2018).
Fig. 1 From ESC/ESH guidelines for hypertension, Eur Heart Journal 2018 (©ESC/ESH 2018)
The ESC/ESH Guidelines (Williams et al. 2018) suggested the following lifestyle changes as contributors for reducing BP and cardiovascular risk to the majority of patients with arterial hypertension: healthy diet including dietary sodium restriction and moderation of alcohol consumption, overweight reduction, regular physical activity, and cessation of consumption of any product containing tobacco or nicotine.

2.1 Salt Restriction

In general, a healthy diet should avoid any excess: moderate sodium reduction is associated with a decrease in BP in hypertensive and normotensive individuals of a maximum of 4.8–2.5 mmHg systolic and 1.9–1.1 mmHg diastolic, respectively (He and MacGregor 2003).

Young patients with hypertension usually are salt-resistant, while older patients as well as obese individuals or patients with diabetes mellitus and chronic kidney disease are characterized by increased salt sensitivity (Weinberger 1996).

Evidence supporting very strong reduction of salt intake is weak. The effect of reduced dietary sodium on cardiovascular event rates remains unclear (Bibbins-Domingo et al. 2010; He et al. 2011; He and MacGregor 2011; Taylor et al. 2011).

Prospective cohort studies have reported an overall increased risk of mortality and cardiovascular events on high sodium intake, but to date, no prospective randomized controlled trial has provided definitive evidence about the optimal sodium intake to minimize cardiovascular events and mortality. However, it was reported that reducing sodium intake below 3 g of sodium per day further reduced BP, but paradoxically was associated with an increased risk of all-cause and cardiovascular mortalities in both the general population and in hypertensive patients, suggesting a J-curve phenomenon (Mente et al. 2016).

Increased potassium intake is associated with BP reduction and may have a protective effect, thereby modifying the association between sodium intake, BP, and CVD. Increasing potassium intake (e.g., including high intake of vegetables and fruits in the diet) could be a problem in patients with diabetes and chronic kidney disease and cannot be applied to all hypertensive patients (Bernabe-Ortiz et al. 2020; Binia et al. 2015; Mente et al. 2016; Miller et al. 2016).

Therefore, every patient with arterial hypertension independently of his/her sodium sensitivity should reduce the sodium consumption and avoid processed and frozen food, which frequently is rich in salt.

2.2 Reduce Alcohol Intake

For a long time, positive linear associations between alcohol consumption, BP, prevalence of hypertension, and cardiovascular risk have been established.

The Prevention and Treatment of Hypertension Study (PATHS) investigated the effects of reduced alcohol consumption on BP; the intervention group had a modest
1.2/0.7 mmHg lower BP than the control group at the end of the 6-month follow-up period. A meta-analysis of 56 epidemiological studies suggested that reduction of alcohol consumption, even for light-moderate drinkers, might be beneficial for cardiovascular health (Holmes et al. 2014). Binge drinking can cause strong increases of BP (Mancia et al. 2013).

Hypertensive men and women, who drink alcohol, should be advised to limit their consumption to 14 units and 8 units per week, respectively (one unit is equal to 125 mL of wine or 250 mL of beer). Alcohol-free days during the week and avoidance of binge drinking are also recommended (Williams et al. 2018).

2.3 Weight Loss and Avoidance of Overweight and Obesity

Weight loss in overweight or obese individuals leads to a significant reduction in BP, independently of exercise and dietary sodium restriction (Appel et al. 2006; Cohen and Gadde 2019), and has multiple beneficial effects against pathologic factors leading to high BP and to end-organ damage in this patient population (Cohen and Gadde 2019).

Weight loss is associated with decreased intra-abdominal pressure exerted on vessels by the excessive visceral fat deposition. Another beneficial effect of weight loss is the amelioration of insulin resistance, which is associated with renal sodium reabsorption and increased sympathetic tone in obesity. Moreover, chronic inflammation associated with overweight/obesity promotes vascular aging, favoring the onset of hypertension. Inflammation also contributes to arterial stiffness and impairs the physiologic anti-contractile effect of perivascular adipocytes on adjacent small arteries (Virdis et al. 2015; Aghamohammadzadeh et al. 2013). Decrease in body weight with lifestyle management, although effective in the short term, is difficult to sustain in the longer-term follow-up. Indeed, the overall efficacy of lifestyle interventions in reducing cardiovascular outcomes has been questioned by the results of the Action for Health in Diabetes (Look AHEAD) Study (Look, Ahead Research Group et al. 2013; Semlitsch et al. 2016). Currently, the most effective pharmacological treatments against obesity include glucagon like peptide-1 (GLP-1) receptor agonists and bariatric surgery. GLP-1 receptor agonists, in particular liraglutide, are cornerstones in antidiabetic therapy, which also have shown positive effects in reducing BP and CVD mortality (Helmstader et al. 2020; Pi-Sunyer et al. 2015; Mingrone et al. 2015). Liraglutide is currently available also as weight-loss medication in obese patients without diabetes and has promising effects improving hypertension and cardiovascular risk profile over 1-year treatment (Pi-Sunyer et al. 2015; Fonseca et al. 2014; le Roux et al. 2017).

Bariatric surgery has a sustained effect on weight loss, which is superior to pharmacological and lifestyle modifications. Considerable weight loss after bariatric surgery corresponds to high rates of remission of hypertension (Pareek et al. 2019). The GATEWAY trial showed that a reduction of \( \geq 30\% \) of the total number of antihypertensive medications while maintaining controlled blood pressure occurred in 83.7\% of the patients randomized to receive the Roux-en-Y gastric bypass plus
antihypertensive medical therapy compared with only 12.8% patients from the control group with pharmacological therapy alone. Indeed, remission of hypertension was present in almost 50% of patients randomized to gastric bypass, whereas no patient randomized to control therapy was free of antihypertensive drugs at 12-month follow-up (Schiavon et al. 2018).

### 2.4 Regular Physical Activity

Epidemiological studies suggest that regular aerobic physical activity is beneficial for both reducing BP and decreasing CVD event rates and mortality (Franklin et al. 2020; Williams et al. 2018). As a result and along with the notion that “more exercise is better,” more and more normotensive and hypertensive adults have increased their participation in high-intensity interval training or competitive long distance endurance events. However, the quality and intensity of the physical activity is very important. Recent evidence suggests that beyond a safe upper limit, exercise may result in deleterious cardiovascular adaptations. For instance, exercise-induced hypertension and the race distances may contribute to the occurrence of myocardial fibrosis detectable by MRI in asymptomatic triathletes (Tahir et al. 2018).

Aerobic endurance training, dynamic resistance training, and isometric training reduce resting systolic BP and diastolic BP by mean 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg, respectively, in general populations. Regular physical activity of lower intensity and duration lowers BP less than moderate- or high-intensity training, but is associated with at least a 15% decrease in mortality in cohort studies (Rossi et al. 2012). Thus, the current ESC/EHS Guidelines recommend at least 30 min of moderate dynamic exercise (walking, jogging, cycling, or swimming) on 5–7 days per week (Williams et al. 2018). The impact of isometric exercises on BP and CVD risk is less well-established, although it can be part of a comprehensive treatment regimen (Chrysant 2010).

### 3 Pharmacological Therapy for the Treatment of Arterial Hypertension

Current evidence suggests that treatment and gradual control of hypertension by the use of the major classes of antihypertensive drugs exert positive effects on atherosclerosis. Randomized controlled trials provided robust evidence that five drug classes lower BP and prevent CVD events. They are therefore recommended by the 2018 ESC/ESH Guidelines (Williams et al. 2018) for the treatment of hypertension: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like diuretics such as chlorthalidone and indapamide). ACE-I or ARBs alone or in combination with a calcium antagonist or a diuretic (thiazide-like to be preferred to thiazide) are considered for the first-line treatment. The use of beta-blockers is limited to special indications.
3.1 Who Should Be Treated with Pharmacological Therapy?

The benefits of antihypertensive therapy are clear in the majority of patients with arterial hypertension, but still controversial in subgroups. They include patients with Grade 1 hypertension but without manifest CVD, patients with white coat or masked hypertension and low cardiovascular risk, patients with an estimated 10-year cardiovascular risk <10%, and patients older than 75 years of age who are non-ambulatory or living in nursing homes.

Randomized trials demonstrated that treating hypertension with any antihypertensive therapy reduces cardiovascular morbidity and mortality. According to the ESC/ESH Guidelines, antihypertensive drug therapy should be initiated without any delay in patients with hypertension Grades 2 or 3 or after some time under non-pharmacological therapy in individuals with very high cardiovascular risk and Grade 1 or high-normal BP (Fig. 1). The decision to initiate drug therapy should be individualized and involve shared decision-making between patient and provider.

3.2 Choice of Initial Antihypertensive Agents

Multiple studies and meta-analyses conclude that the degree of BP reduction rather than the kind of antihypertensive medication is the major determinant of reduction in cardiovascular risk in patients with hypertension (Ettehad et al. 2016).

However, not all antihypertensive drugs are equally effective in reducing cardiovascular events and only few reduced mortality (van Vark et al. 2012).

Recommendations for the use of specific classes of antihypertensive medications are based upon clinical trial evidence of decreased cardiovascular risk, BP-lowering efficacy, safety, and tolerability. Most patients with hypertension will require more than one BP medication to reach their BP goal. As the consequence, the new guideline for treatment of hypertension suggests to use combination therapy at early stage and, if possible, a fixed-dose single-pill combination medication to improve adherence (Williams et al. 2018). Having multiple available classes of BP medications, practitioners and clinicians can individualize therapy based upon individual patient characteristics and preferences.

The following drugs are suggested for the start of monotherapy or combination therapy of arterial hypertension:

- ACE inhibitors
- ARBs
- Long-acting CCBs (most often a dihydropyridine such as amlodipine)
- Thiazide-like or thiazide-type diuretics

The previous 2013 Guidelines (Mancia et al. 2013) favored monotherapy for the start of treating hypertension. However, only a minority of patients reach the target blood pressure level under monotherapy, and the combination of two drugs is much more efficient than increasing the dose of a single drug (Williams et al. 2018).
Therefore, the current 2018 Guidelines limit the start of monotherapy to low-risk patients with stage 1 hypertension whose SBP is $<150$ mmHg, very high-risk patients with high-normal BP, or frail older patients; see Table 1.

### 3.3 Combination Therapy

Single-agent therapy will not adequately control BP in most patients whose baseline systolic BP is 15 mmHg or more above their goal. Combination therapy with drugs from different classes has a substantially greater BP-lowering effect than doubling the dose of a single agent (Wald et al. 2009).

When more than one agent is needed to control BP, a therapy with a long-acting ACE inhibitor or ARB in combination (fix if this is possible) with a long-acting dihydropyridine CCB or a diuretic is the first choice. Combination of an ACE inhibitor or ARBs with a thiazide diuretic is considered less beneficial, when hydrochlorothiazide instead of thiazide-like diuretic (chlorthalidone or indapamide) is used (Burnier et al. 2019; Williams et al. 2018). ACE inhibitors and ARBs should **not** be used together.

Chlorthalidone and indapamide have been used in several RCTs showing cardiovascular benefits, and these agents are more potent per milligram in lowering BP and have a longer duration of action compared with hydrochlorothiazide without any evidence of more side effects (Williams et al. 2018).

As such, even if head-to-head RCTs are missing, this data suggests that thiazide-like diuretics such as chlorthalidone and indapamide should be preferred over classical thiazide diuretics (e.g., hydrochlorothiazide and bendrofluzide) (Williams et al. 2018; Burnier et al. 2019; Roush et al. 2015).

The Danish Cancer Registry and the Danish Prescription Registry examined the association between the use of hydrochlorothiazide (HCTZ) and the risk of basal cell carcinoma, squamous cell carcinoma, and nodular melanoma (Pedersen et al. 2018a, 2018b, 2019). These two case-control studies showed that high cumulative doses of HCTZ ($>50$ g) are associated with a dose-dependent increase in the risk of non-melanoma skin cancer, but not of melanoma. The increase of risk was only small for squamous cell carcinoma and negligible for basal cell carcinoma. These studies have several limitations including the investigation of a pale-skinned population and the lack of information on genetic predisposition, sun habits, and ultraviolet exposure. Moreover, the risk reduction of death due to lower BP by HCTZ was much stronger than the small risk increase for squamous cell carcinoma by HCTZ. In general, statistically significant associations from observational studies do not prove any causal relationship.

The next step is the combination of RAAS blocker, Ca antagonists, and thiazide/thiazide-like diuretics.

If BP is not sufficiently controlled by this triple combination therapy, a mineralocorticoid receptor (MR) antagonist (i.e., spironolactone or eplerenone) may be added (Williams et al. 2015).
In patients with difficult-to-treat/resistant hypertension, a beta-blocker, an alpha-blocker, or a direct arterial vasodilator could be added. Generally, concomitant use of beta-blockers and non-dihydropyridine CCBs should be avoided, as both drug classes reduce heart rate.

3.4 Direct Effects of Antihypertensive Drugs on Atherosclerosis

Apart from lowering blood pressure and thereby removing an important risk factor, some antihypertensive drugs appear to exert direct effects on vascular cells that are involved in the pathogenesis of atherosclerosis.

3.4.1 ARBs and ACE Inhibitors

ARBs and ACE inhibitors directly affect the renin-angiotensin-aldosterone system (RAAS), by blocking the binding of angiotensin II (Ang II) to the AT1 receptor and decreasing the production of Ang II, respectively. Hypertension promotes and accelerates the atherothrombotic process via inflammatory mechanisms linked to activation of oxidative stress by Ang II, which subsequently leads to endothelial dysfunction and development of atherogenic lesions and plaques. Endothelial dysfunction is observed in the early stages of atherosclerosis. A healthy endothelium induces vasodilatation and has antioxidant and anti-thrombotic effects. The dysfunctional endothelium releases less of nitric oxide (NO) and other protective molecules, has a disrupted redox balance, and acquires pro-constrictive and pro-thrombotic phenotypes (Flammer et al. 2012; Sudano et al. 2011). A dysfunctional endothelium has been associated with cardiovascular risk factors including diabetes mellitus or impaired glucose metabolism, hypertension, cigarette smoking, dyslipidemia, obesity, and/or metabolic syndrome (Flammer et al. 2012; Sudano et al. 2011).

RAAS antagonists, as well as some dihydropyridine CCBs, possess ancillary and synergistic effects that increase NO bioavailability, reduce oxidative stress, and suppress inflammatory responses, thereby improving both endothelial activity and vascular function (Safar and Smulyan 2007; Sudano et al. 2011; Taddei et al. 2002).

3.4.2 Diuretics

Among the diuretics, thiazide-like diuretics such chlorthalidone and indapamide but not hydrochlorothiazide were found to improve endothelial function (Dell'Omo et al. 2005; Vinereanu et al. 2014). Indapamide also reduces arterial stiffness (Agnoletti et al. 2013).

3.4.3 Calcium Antagonists

Dihydropyridine CCBs lower BP mainly through vasodilation and reduction of peripheral resistance. Several clinical studies have demonstrated that they have clinical benefits in patients with CVD. Some studies have indicated that dihydropyridine CCBs have anti-atherogenic effects beyond their BP-lowering effects (Silva et al. 2019; Sudano et al. 2011). In fact, in several animal models, dihydropyridine CCBs were found to suppress the formation of atherosclerotic
lesions. It is well-known that the production of reactive oxygen species (ROS) is involved in the progression of atherosclerosis by stimulating the production of inflammatory factors such as chemokines, cytokines, and adhesion molecules (Mason 2002; Ishii et al. 2012). Dihydropyridine CCBs can suppress ROS generation and subsequent inflammatory actions in vascular cells and arterial walls. Furthermore, several reports have revealed that dihydropyridine CCBs suppress the expression of adhesion molecules, thereby inhibiting monocyte adhesion to endothelial cells, which is an early step in the pathogenesis of atherosclerosis. Dihydropyridine CCBs also suppress proliferation and migration of smooth muscle cells both in vitro and in vivo (Mason 2002; Ishii et al. 2012). In macrophages, dihydropyridine CCBs decrease cholesterol accumulation and intracellular cholesterol esterification and increase cholesteryl ester hydrolysis. Moreover, dihydropyridine CCBs suppress the expression of matrix metalloproteinases, which affects the stability of atheromatous plaques. Interestingly, recent studies have revealed that the anti-atherosclerotic effects of dihydropyridine CCBs are mediated, at least in part, via the activation of peroxisome proliferator-activated receptor-γ (Ishii et al. 2012).

3.4.4 Beta-Blockers
In general, beta-blockers usually do not have any effect on endothelial function and atherothrombosis. The only exception is nebivolol, thanks to its high selectivity as beta1-blocker. Nebivolol inhibits the proliferation of human coronary smooth muscle and endothelial cells (Brehm et al. 2001). The specific vasorelaxant properties of nebivolol are mediated by endothelium-dependent NO release and antioxidant activity (do Vale et al. 2018). Unfortunately, nebivolol treatment in patients with non-obstructive coronary artery disease was associated with greater plaque progression and constrictive remodeling as compared to atenolol (Hung et al. 2016). Carvedilol, a nonselective blocker with additional adrenergic receptor antagonist activity, has also been shown to exert beneficial actions against endothelial dysfunction through its antioxidant effects (Bank et al. 2007), although the molecular mechanisms have not yet been fully clarified (Virdis et al. 2011).

3.4.5 Mineralocorticoid Receptor Antagonists
The MR antagonists, spironolactone and eplerenone, have been shown to reduce morbidity and mortality, in part, by blunting the adverse effects of aldosterone on endothelial function and inflammation involved in the development and complications of atherosclerosis. Recent evidence highlight that pharmacological blockade or genetic deletion of endothelial MR blunt vascular inflammation including expression of adhesion molecules, leukocyte-endothelial interactions, and plaque inflammation. Of note, in preclinical studies endothelial MR inhibition is protective only in male, but not in female mice (Moss et al. 2019). Thus, gender- and sex-specific actions of the MR in vascular function and atherosclerosis, so far still poorly investigated, will deserve future attention also in the clinical setting (Shen et al. 2017). Sympathetic hyperactivity with rising catecholamine levels and adrenergic receptors stimulation is a common feature of many CVDs, including

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hypertension. This is associated with endothelial NO synthase uncoupling and a pro-constrictive vascular phenotype on adjacent small arterial vessel wall components, such as smooth muscle and endothelial cells. Activation of MR signaling in the perivascular adipose tissue surrounding small arteries contributes to β-adrenoceptor overstimulation. Thus, MR antagonists targeting the endothelium and the perivascular adipocytes surrounding small arteries may achieve a dual benefit in hypertension with involvement of sympathetic over-activation, as, for instance, in overweight and obesity (Victorio et al. 2016).

4 Perspectives of Future Antihypertensive Therapy

4.1 Unresolved Medical Needs

Despite large evidence confirming the importance of lowering BP and the availability of many effective and well-tolerated antihypertensive drugs, BP control rate is unfortunately not as high as it should. This is, at least in part, related to poor adherence to lifelong antihypertensive therapy but also, in a minority of patients, due to “difficult to treat” or “resistant” hypertension.

According to the guidelines, resistant or difficult-to-treat hypertension is defined as: blood pressure that is not controlled to goal despite adherence to an appropriate regimen of three antihypertensive drugs of different classes (including a diuretic) in which all drugs are prescribed at suitable antihypertensive doses (Williams et al. 2018). Pseudo-resistance as well as secondary causes of hypertension should be excluded before this diagnosis is made.

Inaccurate blood pressure measurement (e.g., use of an inappropriately small blood pressure cuff, not allowing a patient to rest quietly before taking readings)

Poor adherence to blood pressure medications

Poor adherence to lifestyle and dietary approaches to lower blood pressure

Suboptimal antihypertensive therapy, due either to inadequate doses, an inappropriate drug combination, or exclusion of a diuretic from the antihypertensive regimen

White coat hypertension

Extracellular volume expansion

Increased sympathetic activation

Ingestion of substances that can elevate the blood pressure, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or stimulants

Secondary or contributing causes of hypertension
4.2 New Drug Developments

Recent research has not yielded major advances in treatment of hypertension: no new targets were identified for development of antihypertensive drugs. In fact, trends show a dramatic slowing of research and development for novel blood pressure-lowering drugs. The reasons are manifold: the field is crowded with relatively effective drugs; there is a lack of major new discoveries and targets; and there are many challenges in developing blockbuster drugs. A short look in clinicaltrial.gov shows that while the development of new classes of antihypertensive drugs is apparently waning, the most current activities by big pharmaceutical companies focused on developing new combination pills, including fixed-dose combination drugs with the exception of a new ARB (fimasartan) and the compound AGSCT101, which is actually tested versus carvedilol. Fimasartan is an Ang II receptor antagonist with selectivity for the AT-1 receptor subtype, developed in 2012 by a Korean company (Boryung Pharmaceutical) as an oral antihypertensive drug (Fimasartan 2011; Chi et al. 2011). Fimasartan reduced BP with a good tolerability profile in a large-scale observational population study – Safe-KanArb (Park et al. 2013). The K-MetS study (Park et al. 2017) included 10,601 patients with metabolic syndrome and evaluated long-term effects of fimasartan on major adverse cardiovascular outcomes.

A recent study evaluated the effects of fimasartan and amlodipine therapy on carotid atherosclerotic plaque inflammation using 18F-fluorodeoxyglucose positron emission tomography imaging. Both drugs similarly decreased carotid atherosclerotic plaque inflammation in patients with acute coronary syndrome (Oh et al. 2019).

Concerning AGSCT101, a new antihypertensive drug developed by Ahn-Gook Pharmaceuticals Co., Ltd., the details are scarce. The Phase III Clinical Trial to Evaluate the Antihypertensive Effect of AGSCT101 Versus Carvedilol in Patient with Stage 1 to 2 Essential Hypertension is described in clinicaltrial.gov. Unfortunately, data about mechanism of action of this drug and status of recruiting of the described study are missing.

4.3 Device Therapy

Various device-based therapies such as renal denervation, carotid baroreceptor stimulation, creation of an arteriovenous fistula, or endovascular carotid body modification have emerged, principally targeted at the treatment of resistant hypertension.

Most data are available for renal denervation. The principle of renal denervation is to destroy some of the sympathetic nerves around the renal artery leading to lower sympathetic nervous activity and lower BP. The first results on renal denervation were obtained with devices using radiofrequency application in the open label SYMPLICITY HTN-1 and SYMPLICITY HTN-2 trials, along with several case series and observational studies. The SYMPLICITY HTN-3 trial proved safety, but was unable to show efficacy of renal denervation using a radiofrequency catheter when...
compared with sham treatment in patients with severe resistant hypertension on multiple medications (Williams et al. 2018). Post hoc analyses of the SYMPLICITY HTN-3, however, revealed important information concerning patient selection, difference in adherence to antihypertensive medication in the treatment groups, a higher use of antihypertensive drugs in the sham group, as well as technical failure in performing renal denervation, which led to a revision of renal denervation technology and technique. Based on this background, several novel, sham-controlled studies have been conducted and are, in part, published. SPYRAL HTN-OFF MED (Townsend et al. 2017; Bohm et al. 2020), SPYRAL HTN-ON MED (Kandzari et al. 2018), as well as RADIANCE-HTN SOLO (Azizi et al. 2018) showed significant and consistent reductions in BP, both office and ambulatory, in patients with and without concomitant antihypertensive.

The SPYRAL HTN-ON MED was recently published and showed the superiority of catheter-based renal denervation compared with a sham procedure to safely lower BP in the absence of antihypertensive medications (Bohm et al. 2020). Catheter-based renal denervation is superior to a sham procedure to safely lower BP in the absence of antihypertensive medications.

Less data are available about the effect of carotid baroreceptor stimulation and endovascular carotid body modification both techniques aiming to reduce BP through reduction of sympathetic tone and obtained by creation of an arteriovenous fistula. Concerning carotid baroreceptor stimulation, the first-generation device reduced BP in controlled and uncontrolled clinical trials, while controlled clinical trials proving efficacy in BP reduction do not exist for the currently available second-generation carotid sinus stimulator (Jordan et al. 2019; Heusser et al. 2020).

Some, mostly uncontrolled, studies suggest that other techniques such as baroreflex amplification and carotid body modulation may lead to reduction of BP in patients with difficult-to-treat hypertension. However more evidence on safety and efficacy from ongoing large randomized sham-controlled trials is needed before baroreflex amplification and carotid body modulation can be implemented in routine clinical practice (Groenland and Spiering 2020).

Last, but not least, the possibility to safely reduce BP in patients with uncontrolled hypertension by creating a central iliac arteriovenous anastomosis was tested. The ROX CONTROL HTN study (Lobo et al. 2015) tested this hypothesis using the novel arteriovenous ROX Coupler (ROX Medical, San Clemente, CA, USA).

This small study (44 patients treated and 39 patients in the standard of care group) enrolled and showed that creation of an arteriovenous anastomosis was associated with significantly reduced BP.

The actual ESC/ESH Guidelines do not recommend the use of any device-based therapies for the routine treatment of hypertension, unless in the context of clinical studies and RCTs (Williams et al. 2018).

Nevertheless, device-based therapy for hypertension is a fast-moving field, and new data especially data from study evaluating renal denervation are expected in the near future and could change this recommendation.
5 Conclusion

Hypertension represents one of the most important modifiable risk factors for stroke, heart failure, myocardial infarction, and chronic kidney disease, contributing significantly to the global burden of CVD.

The initial assessment of a patient with hypertension is essential for choosing effective therapy. All cardiovascular risk factors as well as hypertension-mediated target organ damage and presence of comorbidities should be taken into account.

The treatment of hypertension should focus on the overall health of the patient, focusing on reducing the risk of future cardiovascular events.

For a long-lasting adherence, it is important that patients are actively involved in the process of choosing the best BP-lowering strategies.

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References

Aghamohammadzadeh R, Greenstein AS, Yadav R, Jeziorska M, Hama S, Soltani F, Pemberton PW, Ammori B, Malik RA, Soran H, Heagerty AM (2013) Effects of bariatric surgery on human small artery function: evidence for reduction in perivascular adipocyte inflammation, and the restoration of normal anticontractile activity despite persistent obesity. J Am Coll Cardiol 62:128–135

Agnoletti D, Zhang Y, Borghi C, Blacher J, Safar ME (2013) Effects of antihypertensive drugs on central blood pressure in humans: a preliminary observation. Am J Hypertens 26:1045–1052

Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM, Association American Heart (2006) Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension 47:296–308

Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, Saxena M, Feyz L, Rader F, Lurz P, Sayer J, Sapoval M, Levy T, Sanghvi K, Abraham J, Sharp ASP, Fisher NDL, Bloch MJ, Reeve-Stoffer H, Coleman L, Mullin C, Mauri L, Radiance-HTn Investigators (2018) Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet 391:2335–2345

Bank AJ, Kelly AS, Thelen AM, Kaiser DR, Gonzalez-Campoy JM (2007) Effects of carvedilol versus metoprolol on endothelial function and oxidative stress in patients with type 2 diabetes mellitus. Am J Hypertens 20:777–783

Bernabe-Ortiz A, Rosas Y, Sal VG, Ponce-Lucero V, Cardenas MK, Carrillo-Larco RM, Diez-Cansco F, Pesantes MA, Sacksteder KA, Gilman RH, Miranda JJ (2020) Effect of salt substitution on community-wide blood pressure and hypertension incidence. Nat Med 26:374

Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L (2010) Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 362:590–599

Binia A, Jaeger J, Hu Y, Singh A, Zimmermann D (2015) Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: a meta-analysis of randomized controlled trials. J Hypertens 33:1509–1520
Bohm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, Tsioufis K, Pocock S, Konstantinidis D, Choi JW, East C, Lee DP, Ma A, Ewen S, Cohen DL, Wilensky R, Devireddy CM, Lea J, Schmid A, Weil J, Agdirligotlu T, Reedus D, Jefferson BK, Reyes D, D’Souza R, Sharp ASP, Sharif F, Fahy M, deBruin V, Cohen SA, Brar S, Townsend RR, Spyral Htn-Off Med Pivotal Investigators (2020) Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED pivotal): a multicentre, randomised, sham-controlled trial. Lancet

Brehm BR, Wolf SC, Bertsch D, Klaussner M, Wesselborg S, Schuler S, Schulze-Osthoff K (2001) Effects of nebivolol on proliferation and apoptosis of human coronary artery smooth muscle and endothelial cells. Cardiovasc Res 49:430–439

Burnier M, Bakris G, Williams B (2019) Renal denervation in hypertension: an update. J Nephrol 32:343–357

Chi YH, Lee H, Paik SH, Lee JH, Yoo BW, Kim JH, Tan HK, Kim SL (2011) Safety, tolerability, pharmacokinetics, and pharmacodynamics of fimasartan following single and repeated oral administration in the fasted and fed states in healthy subjects. Am J Cardiovasc Drugs 11:335–346

Chrysant SG (2010) Current evidence on the hemodynamic and blood pressure effects of isometric exercise in normotensive and hypertensive persons. J Clin Hypertens (Greenwich) 12:721–726

Cohen JB, Gadde KM (2019) Weight loss medications in the treatment of obesity and hypertension. Curr Hypertens Rep 21:16

Dell'Omo G, Penno G, Del Prato S, Pedrinelli R (2005) Chlorthalidone improves endothelial-mediated vascular responses in hypertension complicated by nondiabetic metabolic syndrome. J Cardiovasc Pharmacol Ther 10:265–272

do Vale GT, Simplicio JA, Gonzaga NA, Yokota R, Ribeiro AA, Casarin DE, de Martinis BS, Tirapelli CR (2018) Nebivolol prevents vascular oxidative stress and hypertension in rats chronically treated with ethanol. Atherosclerosis 274:67–76

Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 387:957–967

Fimasartan (2011) Am J Cardiovasc Drugs 11:249–252

Flammer AJ, Anderson T, Celemeraj DS, Creager MA, Deanfield J, Ganz P, Hamburg NM, Luscher TF, Shechter M, Taddei S, Vita JA, Lerman A (2012) The assessment of endothelial function: from research into clinical practice. Circulation 126:753–767

Fonseca VA, Deevies JR, Henry RR, Donsmark M, Thomsen HF, Plutzky J (2014) Reductions in systolic blood pressure with liraglutide in patients with type 2 diabetes: insights from a patient-level pooled analysis of six randomized clinical trials. J Diabetes Complicat 28:399–405

Franklin BA, Thompson PD, Al-Zaiti SS, Albert CM, Hivert MF, Levine BD, Lobelo F, Madan K, Sharrief AZ, Eijsvogels TMH, Lifestyle American Heart Association Physical Activity Committee of the Council on, Health Cardiometabolic, Cardiovascular Council on, Nursing Stroke, Cardiology Council on Clinical, and Council Stroke (2020) Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective-an update: a scientific statement from the American Heart Association. Circulation:CIR0000000000000749

Groenland EH, Spiering W (2020) Baroreflex amplification and carotid body modulation for the treatment of resistant hypertension. Curr Hypertens Rep 22:27

He FJ, MacGregor GA (2003) How far should salt intake be reduced? Hypertension 42:1093–1099

He FJ, MacGregor GA (2011) Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. Lancet 378:380–382

He FJ, Burnier M, Macgregor GA (2011) Nutrition in cardiovascular disease: salt in hypertension and heart failure. Eur Heart J 32:3073–3080

Helmstadter J, Frenis K, Filippou K, Grill A, Dib M, Kalinovic S, Pawelke F, Kus K, Kroller-Schon S, Oelze M, Chlopicki S, Schuppan D, Wenzel P, Ruf W, Drucker DJ, Munzel T, Daiber A, Steven S (2020) Endothelial GLP-1 (glucagon-like Peptide-1) receptor mediates...
cardiovascular protection by Liraglutide in mice with experimental arterial hypertension. Arterioscler Thromb Vasc Biol 40:145–158

Heusser K, Thone A, Lipp A, Menne J, Beige J, Reuter H, Hoffmann F, Halbach M, Eckert S, Wallbach M, Koszolek M, Haarmann H, Joyner MJ, Paton JFR, Diedrich A, Haller H, Jordan J, Tank J (2020) Efficacy of electrical Baroreflex activation is independent of peripheral chemoreceptor modulation. Hypertension 75:257–264

Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, Prieto-Merino D, Dehghan A, Trompet S, Wong A, Cavadino A, Drogan D, Padmanabhan S, Li S, Yesupriya A, Leusink M, Sundstrom J, Hubacek JA, Pikhart H, Scharfetter C, Gamble DM, Rayaprolu S, Ross OA, McAllan S, Vikhrieva O, Sluijs I, Scott RA, Adamkova F, Flicker L, Bockxmeer FM, Power C, Marques-Vidal P, Meade T, Marmot MG, Ferro JM, Pauloos-Pinheiro S, Humphries SE, Talmud PJ, Mateo Leach I, Verweij N, Linneberg A, Skaaby T, Dovesendans PA, Kramer MJ, van der Harst P, Klungel OH, Dowling NF, Dominiczak AF, Kumari M, Nicolaides AN, Weikert C, Boeing H, Ebrahim S, Gaunt TR, Price JF, Lannfelt L, Peasey A, Kabubina R, Pajak A, Malyutina S, Voevoda MI, Tamosiunas A, Matiilan-van der Zee AH, Norman PE, Hankey GJ, Bergmann MM, Hofman A, Franco OH, Cooper J, Palmen J, Spiering W, de Jong PA, Kuhl D, Hardy R, Uitterlinden AG, Ikram MA, Ford I, Hypponen E, Almeida OP, Wareham NJ, Khaw KT, Hamsten A, Husemeoen LL, Tjonneland A, Tolstrup JS, Rimm E, Beulens JW, Verschuren WM, Onland-Moret NC, Hofker MH, Wannamethee SG, Whincup PH, Morris R, Vicente AM, Watkins H, Furrall M, Jukema JW, Meschia J, Cupples LA, Sharp SJ, Fornage M, Kooperberg C, LaCroix AZ, Dai JY, Lanktree MB, Siscovick DS, Jorgenson E, Spring B, Coresh J, Li YR, Buxbaum SG, Schreiner PJ, Ellison RC, Tsai MY, Patel SR, Redline S, Johnson AD, Hoogeveen RC, Hakonarson H, Rotter JI, Boerwinkle E, de Bakker PI, Kivimaki M, Asselbergs FW, Sattar A, Lawlor DA, Whittaker J, Davey Smith G, Mukamal K, Psaty BM, Wilson JG, Lange LA, Hamidovic A, Hingorani AD, Nordestgaard BG, Bobak M, Leon DA, Langenberg C, Palmer TM, Reiner AP, Keating BJ, Dudbridge F, Casas JP, Consortium InterAct (2014) Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ 349:g4164

Hung OY, Molony D, Corban MT, Rasoul-Arzrumly E, Maynard C, Eshtehardi P, Dhawan S, Timmins LH, Piccellini M, Ahn SG, Gogas BD, McDaniel MC, Quyyumi AA, Giddens DP, Samady H (2016) Comprehensive assessment of coronary plaque progression with advanced intravascular imaging, physiological measures, and wall shear stress: a pilot double-blinded randomized controlled clinical trial of Nebivolol versus atenolol in nonobstructive coronary artery Disease. J Am Heart Assoc 5

Ishii N, Matsumura T, Shimoda S, Araki E (2012) Anti-atherosclerotic potential of dihydropyridine calcium channel blockers. J Atheroscler Thromb 19:693–704

Jordan J, Tank J, Reuter H (2019) Carotid baroreceptor stimulation. In: Mancia G, Dobrabantu M, Grassi G, Voicu V (eds) Hypertension and heart failure. Springer, Cham

Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S, Cohen SA, Fahy M, Pilcher G, Kario K, Spyral Htn-On Med Trial Investigators (2018) Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet 391:2346–2355

le Roux C, Aroda V, Hemmingsson J, Cancino AP, Christensen R, Pi-Sunyer X (2017) Comparison of efficacy and safety of Liraglutide 3.0 mg in individuals with BMI above and below 35 kg/m (2): a post-hoc analysis. Obes Facts 10:531–544

Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, Ng GA, Ott C, Schmied RE, Rox Control Htn Investigators (2015) Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CON TROL HTN study): a randomised controlled trial. Lancet 385:1634–1641
Look, Ahead Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 369:145–154

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhoff P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waerbeek, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Cufi V, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Heseltine D, Hoes AW, Kirchhoff P, Knutti J, Kolp P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendler M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendler M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hilti JB, Cufi V, De Buyzere M, De Geest S, Derruemeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerv C, Gerv C, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic V, Mahrothild H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struikker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA (2013) 2013 ESH/ESC guidelines for the management of Arterial Hypertension: the task force for the management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34:2159–2219

Mason RP (2002) Mechanisms of plaque stabilization for the dihydropyridine calcium channel blocker amloplin: review of the evidence. Atherosclerosis 165:191–199

Mente A, O’Donnell M, Ranganarjan S, Dagenais G, Lear S, McQueen M, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, Li W, Lu Y, Yi S, Rensheng L, Eqbal R, Mony P, Yusuf R, Yusof K, Szuba A, Oegy A, Rosengren A, Bahonar A, Yusufali A, Schutte AE, Chifamba J, Mann GF, Anand SS, Teo K, Yusuf S, Epidream Pure, and Ontarget Transcend Investigators (2016) Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 388:465–475

Miller V, Yusuf S, Chow CK, Dehghan M, Corsi DJ, Lock K, Popkin B, Ranganarjan S, Khatib R, Lear SA, Mony P, Kaur M, Mohan V, Vijayakumar K, Gupta R, Kruger A, Tsolekile L, Mohammadifar N, Rahbar N, Rosengren A, Avezum A, Orlandini A, Iqbal R, Lopez-Jaramillo P, Yusufali A, Karsidag K, Iqbal R, Chifamba J, Oakley SM, Anand SS, Teo K, Mehta A (2016) Availability, affordability, and consumption of fruits and vegetables in 18 countries across income levels: findings from the prospective urban rural epidemiology (PURE) study. Lancet Glob Health 4:e695–e703

Mingrone G, Panunzi S, de Gaetano A, Guidone C, Iaconelli A, Nanni G, Castagneto M, Bornstein S, Rubino F (2015) Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 386:964–973

Moss ME, Lu Q, Iyer SL, Engelbertsen D, Marzolla V, Caprio M, Lichtman AH, Jaffe IZ (2019) Endothelial mineralocorticoid receptors contribute to vascular inflammation in atherosclerosis in a sex-specific manner. Arterioscler Thromb Vasc Biol 39:1588–1601

Oh M, Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Moon DH, Park SW, Park SJ (2019) Comparison of fimasartan and amloplin therapy on carotid atherosclerotic plaque inflammation. Clin Cardiol 42:241–246
Pareek M, Bhatt DL, Schiavon CA, Schauer PR (2019) Metabolic surgery for hypertension in patients with Obesity. Circ Res 124:1009–1024

Park JB, Sung KC, Kang SM, Cho EJ (2013) Safety and efficacy of fimasartan in patients with arterial hypertension (safe-KanArb study): an open-label observational study. Am J Cardiovasc Drugs 13:47–56

Park JB, Kim SA, Sung KC, Kim JY (2017) Gender-specific differences in the incidence of microalbuminuria in metabolic syndrome patients after treatment with fimasartan: the K-MetS study. PLoS One 12:e0189342

Pedersen SA, Gaist D, Schmidt SAJ, Holmich LR, Friis S, Pottegard A (2018a) Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol 78(673–81):e9

Pedersen SA, Schmidt SAJ, Klausen S, Pottegard A, Friis S, Holmich LR, Gaist D (2018b) Melanoma of the skin in the Danish Cancer registry and the Danish melanoma database: a validation study. Epidemiology 29:442–447

Pedersen SA, Johannesdottir Schmidt SA, Holmich LR, Friis S, Pottegard A, Gaist D (2019) Hydrochlorothiazide use and risk for Merkel cell carcinoma and malignant adnexal skin tumors: a nationwide case-control study. J Am Acad Dermatol 80(460–65):e9

Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP, Scale Obesity, and N. N. Study Group Prediabetes (2015) A randomized, controlled trial of 3.0 mg of Liraglutide in weight management. N Engl J Med 373:11–22

Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS (2012) The impact of physical activity on mortality in patients with high blood pressure: a systematic review. J Hypertens 30:1277–1288

Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA (2015) Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. Hypertension 65:1041–1046

Safar ME, Smulyan H (2007) Atherosclerosis, arterial stiffness and antihypertensive drug therapy. Adv Cardiol 44:331–351

Schiavon CA, Bersch-Ferreira AC, Santucci EV, Oliveira JD, Torreglosa CR, Bueno PT, Frayha JC, Santos RN, Damiani LP, Noujaim PM, Halpern H, Monteiro FLJ, Cohen RV, Uchoa CH, de Souza MG, Amodeo C, Bortolotto L, Ikeoka D, Drager LF, Cavalcanti AB, Berwanger O (2018) Effects of bariatric surgery in obese patients with hypertension: the GATEWAY randomized trial (gastric bypass to treat obese patients with steady hypertension). Circulation 137:1132–1142

Semlitsch T, Jeitler K, Berghold A, Horvath K, Posch N, Poggenburg S, Siebenhofer A (2016) Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev 3:CD008274

Shen ZX, Chen XQ, Sun XN, Sun JY, Zhang WC, Zheng XJ, Zhang YY, Shi HJ, Zhang JW, Li C, Wang J, Liu X, Duan SZ (2017) Mineralocorticoid receptor deficiency in macrophages inhibits atherosclerosis by affecting foam cell formation and Efferocytosis. J Biol Chem 292:925–935

Silva IVG, de Figueiredo RC, Rios DRA (2019) Effect of different classes of antihypertensive drugs on endothelial function and inflammation. Int J Mol Sci 20:3458

Sudano I, Roas S, Noll G (2011) Vascular abnormalities in essential hypertension. Curr Pharm Des 17:3039–3044

Taddei S, Virdis A, Ghidoni L, Sudano I, Salvetti A (2002) Effects of antihypertensive drugs on endothelial dysfunction: clinical implications. Drugs 62:265–284

Tahir E, Starekova J, Muellerleile K, von Stritzky A, Munch J, Avanesov M, Weinrich JM, Stehning C, Bohnen S, Radunski UK, Freiwald E, Blankenberg S, Adam G, Pressler A, Patten M, Lund GK (2018) Myocardial fibrosis in competitive triathletes detected by contrast-enhanced CMR correlates with exercise-induced hypertension and competition history. JACC Cardiovasc Imaging 11:1260–1270
Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S (2011) Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). Am J Hypertens 24:843–853

Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsiofis K, Tousoulis D, Sharp ASP, Watkinson AF, Schmieder RE, Schmid A, Choi JW, East C, Walton A, Hopper I, Cohen DL, Wilensky R, Lee DP, Ma A, Devireddy CM, Lea JP, lurz PC, Fengler K, Davies J, Chapman N, Cohen SA, DeBruin V, Fahy M, Jones DE, Rothman M, Bohm M, Spyril Htn-Off Med trial investigators (2017) Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPY RAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 390:2160–2170

van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, Boersma E (2012) Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J 33:2088–2097

Vicario JA, Clerici SP, Palacios R, Alonso MJ, Vassallo DV, Jaffe IZ, Rossoni LV, Davel AP (2016) Spironolactone prevents endothelial nitric oxide synthase uncoupling and vascular dysfunction induced by beta-adrenergic overstimulation: role of perivascular adipose tissue. Hypertension 68:726–735

Vinereanu D, Dulgheru R, Magda S, Dragoi Galrinho R, Florescu M, Cinteza M, Granger C, Ciobanu AO (2014) The effect of indapamide versus hydrochlorothiazide on ventricular and arterial function in patients with hypertension and diabetes: results of a randomized trial. Am Heart J 168:446–456

Virdis A, Ghiadoni L, Taddei S (2011) Effects of antihypertensive treatment on endothelial function. Curr Hypertens Rep 13:276–281

Virdis A, Duranti E, Rossi C, Dell’Agnello U, Santini E, Anselmino M, Chiarugi M, Taddei S, Solini A (2015) Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue. Eur Heart J 36:784–794

Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ (2009) Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 122:290–300

Weinberger MH (1996) Salt sensitivity of blood pressure in humans. Hypertension 27:481–490

Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ, Pathway Studies Group British Hypertension Society’s (2015) Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 386:2059–2068

Williams B, Mancia G, Spiering W, Agabiti Roselli E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsiofis C, Aboyans V, Desormais I, E. S. C. Scientific Document Group (2018) 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 39:3021–3104
