Consensus Document

Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and difficult to treat arterial hypertension

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Obese patients are prone to arterial hypertension, require more antihypertensive medications, and have an increased risk of treatment-resistant arterial hypertension. Obesity-induced neurohumoral activation appears to be involved. The association between obesity and hypertension shows large inter-individual variability, likely through genetic mechanisms. Obesity affects overall cardiovascular and metabolic risk; yet, the relationship between obesity and cardiovascular risk is complex and not sufficiently addressed in clinical guidelines. The epidemiological observation that obesity may be protective in patients with established cardiovascular disease is difficult to translate into clinical experience and practice. Weight loss is often recommended as a means to lower blood pressure. However, current hypertension guidelines do not provide evidence-based guidance on how to institute weight loss. In fact, weight loss influences on blood pressure may be overestimated. Nevertheless, weight loss through bariatric surgery appears to decrease cardiovascular risk in severely obese patients. Eventually, most obese hypertensive patients will require antihypertensive medications. Data from large-scale studies with hard clinical endpoints on antihypertensive medications specifically addressing obese patients are lacking and the morbidity from the growing population of severely obese patients is poorly recognized or addressed. Because of their broad spectrum of beneficial effects, renin-angiotensin system inhibitors are considered to be the most appropriate drugs for antihypertensive treatment of obese patients. Most obese hypertensive patients require two or more antihypertensive drugs. Finally, how to combine weight loss strategies and antihypertensive treatment to achieve an optimal clinical outcome is unresolved.

Keywords: bariatric surgery, cardiovascular risk, hypertension, neurohumoral, obesity, obesity paradox, treatment resistance

Abbreviations: EASO, European Association for the Study of Obesity; ESH, European Society of Hypertension

INTRODUCTION

Obesity and arterial hypertension frequently coexist in the same patient. In a recent survey in Germany, approximately 75% of the hypertensive patients seen by general practitioners or internists were overweight or obese [1]. Hence, mechanisms through which obesity promotes arterial hypertension have been intensely investigated by basic and clinical scientists over the past decades. Moreover, the concept that obesity and arterial hypertension can be additive in terms of cardiovascular risk is widely appreciated. Yet, clinical decision-making in obese patients is complicated by a surprising lack of evidence on the relative importance of obesity and hypertension treatment and its efficacy and safety. The European Association for the Study of Obesity (EASO) and the European Society of Hypertension (ESH) organized joint scientific sessions during their yearly meetings to address this issue. The present joint scientific statement provides an overview on the interaction between obesity and arterial hypertension from a pathophysiological, epidemiological, and clinical point of view. An important goal of this joint effort is to identify areas of uncertainty that ought to be studied in more detail. In particular, a focus is made on difficulties in treating hypertension in these patients.

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HOW OBESITY RAISES BLOOD PRESSURE

Whereas much of the arterial hypertension in lean persons is driven by an increase in peripheral vascular resistance, obesity-associated hypertension is often characterized by increased cardiac output [2,3]. The increase in cardiac output appears to be mediated in part through plasma volume expansion and sodium retention [4]. Neurohumoral mechanisms are also involved [5].

Pharmacological studies [6,7] and direct sympathetic nerve recordings [8] suggest that the sympathetic nervous system may be overactivated in obesity-associated arterial hypertension. However, sympathetic activation in obese individuals is not uniform. In obese normotensive individuals, sympathetic outflow to the kidney is increased, whereas sympathetic outflow to the heart is reduced. In contrast, obese hypertensive patients exhibit an increase in both renal and cardiac sympathetic activity [9]. Baroreflex dysfunction and the obstructive sleep apnea (OSA) syndrome, a common comorbidity of obesity, may also contribute to sympathetic overactivity [8,10,11]. The relevance of sympathetic activation is highlighted by recent studies demonstrating a strong association with obesity-induced subclinical cardiovascular organ damage in young adults [12]. Even though plasma volume and sodium retention are increased, the systemic renin–angiotensin–aldosterone system is activated in obesity [13]. Weight loss studies suggest that the local renin-angiotensin system in adipose tissue may contribute to the increase in systemic renin-angiotensin system activity [14].

The mechanisms through which increased adiposity increases neurohumoral activity in humans are not fully understood and some evidence conflicts. Animal studies suggest that signaling molecules produced in adipose tissue, such as leptin, may increase sympathetic activity through the hypothalamic melanocortin pathway [15,16]. Remarkably, however, human monogenic obesity caused by leptin deficiency is associated with signs and symptoms of reduced sympathetic activity [17]. Furthermore, hypertension risk, blood pressure, and urinary norepinephrine excretion are reduced in overweight and obese patients with genetic melanocortin 4 receptor deficiency compared with equally overweight control individuals [18]. Hyperinsulinemia may also promote neurohumoral activation [19]. Conversely, sympathetically mediated vasoconstriction may worsen muscular insulin sensitivity by decreasing glucose and insulin delivery [20].

In addition to neurohumoral activation, obese animals showed structural kidney changes that may further augment sodium retention [21]. Fat accumulation in the renal sinus, a so-called fatty kidney, can occur in human obesity. Individuals with fatty kidney exhibit an increased risk of arterial hypertension even after adjustment for body mass index (BMI) or abdominal visceral adipose tissue [22].

EPIDEMIOLOGICAL ASSOCIATION BETWEEN OBESITY AND ARTERIAL HYPERTENSION

Large-scale epidemiological studies in different countries support the association between obesity and arterial hypertension which appears to be established already at age 8–11 [23]. In the third National Health and Nutrition Examination Survey (NHANES III), hypertension risk was increased in overweight men and women and more so in those who were obese [24]. Among one million participants in the Community Hypertension Evaluation, the frequency of hypertension in overweight individuals aged 20–39 years was doubled compared with normal-weight participants [25]. In the Framingham Heart Study, the age-adjusted relative risk for new onset of arterial hypertension compared with normal-weight participants was 1.75 and 1.46 for overweight men and women, respectively [26]. In African-American women, the odds of having arterial hypertension increased steeply with a BMI exceeding 23 kg/m^2. In the Japanese Tanno-Sobetsu study, abdominal obesity increased the risk of developing arterial hypertension by 2.33 [27]. Regression models corrected for the age-related rise in blood pressure demonstrated an increase in systolic blood pressure of 1 mmHg for a gain of 1.7 kg/m^2 and 4.5 cm in men or 1.3 kg/m^2 and 2.5 cm in women in BMI or waist circumference, respectively [28]. In a Chinese population, both systolic and diastolic blood pressures were positively correlated with BMI [29]. For each 1 kg/m^2 increase in BMI blood pressure increased by 1.47/1.13 mmHg. Remarkably, obesity, hypertension, and the aging-associated rise in blood pressure were virtually absent in a rural population of southern Chinese Yi farmers [29]. A more recent study conducted in Beijing suburbs substantiates these findings [30].

Differences in body fat distribution may modulate the correlation between BMI and blood pressure. In the cross-sectional Health, Aging, and Body Composition Study, visceral adipose tissue was strongly associated with the presence of arterial hypertension [31]. The association was strongest in individuals with low total body fat. In the Framingham Heart Study Multidetector Computed Tomography Study, visceral and subcutaneous abdominal adipose tissue showed a similar effect on systolic blood pressure. In men, systolic blood pressure increased 3.3 mmHg for each 1 standard deviation (SD) increase of visceral adipose tissue and 2.3 mmHg for each SD increase in subcutaneous adipose tissue [32]. A multivariable-adjusted linear regression analysis in another study showed that blood pressure was 1.3/1.36 mmHg higher in men for each 1 SD increment in visceral adipose tissue [33]. In the same analysis, visceral adipose tissue was not related to blood pressure in women. Similarly, abdominal adiposity had a stronger effect on sympathetic activity in men than in women [34].

In addition to sex, genetic factors modulate blood pressure responses to increasing adiposity. For example, in Pima Indians, blood pressure does not increase with increasing adiposity as it does in Western societies [35]. The observation suggests that some persons may have a 'fat-sensitive' blood pressure, because blood pressure increases with increasing adiposity. Others, such as many Pima Indians, appear 'fat-resistant' with regard to their blood pressure. Regardless of the variability in the relationship between adiposity and blood pressure, obesity causes or worsens arterial hypertension in a large number of susceptible individuals.

OBESITY AS A CAUSE OF TREATMENT-RESISTANT ARTERIAL HYPERTENSION

Treatment-resistant refractory arterial hypertension is usually diagnosed when prescription of three sufficiently dosed antihypertensive drugs including a diuretic fails to achieve systolic and diastolic blood pressure control [36,37]. Whereas current European guidelines for the management of arterial hypertension do not specifically address the issue [36], recent studies suggest obesity as an important cause of treatment resistance. A German survey conducted in the primary care setting showed that obese hypertensive patients are often prescribed more antihypertensive medications. Yet, their blood pressure tends to be less well controlled compared with normal-weight hypertensive patients [1]. Similarly, obese participants from the Framingham Offspring and Third Generation cohort were more likely to receive antihypertensive medication than normal-weight or overweight participants [38]. Yet, blood pressure control was similar among these groups. The prospective Vascular Protection and Guideline Orientated Approach to Lipid Lowering Registries recruited 7357 high-risk vascular Canadian outpatients in Canada from 2001 to 2004 [39]. A BMI of at least 30 kg/m^2 decreased the likelihood of having blood pressure controlled to below 140/90 mmHg in non-diabetic or to below 130/80 mmHg in diabetic patients. Among participants of the Framingham Heart Study, presence of obesity defined as BMI of at least 30 kg/m^2 was the strongest predictor of lack of diastolic blood pressure control below 90 mmHg and the second strongest predictor of lack of systolic blood pressure control below 140 mmHg [40]. Similarly, patients with a BMI of at least 30 kg/m^2 in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) required more antihypertensive medications and were nevertheless less likely having their blood pressure controlled [41]. A recent analysis of the NHANES identified characteristics associated with apparent treatment-resistant arterial hypertension between 1988–1994, 1999–2004, and 2005–2008 [42]. Apparent treatment-resistant arterial hypertension was defined as blood pressure of at least 140/90 mmHg when patients reported taking at least three antihypertensive drugs. In a multivariable logistic regression analysis, obesity was consistently and independently associated with apparent treatment-resistant hypertension [42]. Overall, obesity appears to be an important cause of treatment-resistant arterial hypertension in the primary care setting, among high-risk patients, and in clinical trials. The association between obesity and treatment-resistant arterial hypertension may be mediated at least in part through OSA, volume expansion, inappropriately high plasma aldosterone concentrations, and sympathetic activation [5,43,44], which are all more likely to be present in obese patients.

OBESITY AND HYPERTENSION INTERACTIONS ON CARDIOVASCULAR RISK

Obesity can drive an increase in blood pressure. In addition, obesity affects overall cardiovascular and metabolic risk. For many years, blood pressure values dominated risk assessment and treatment decisions in hypertension guidelines. The 2007 European Society of Hypertension Guidelines for the Management of Arterial Hypertension emphasized the need to relate diagnosis and management of arterial hypertension to total cardiovascular risk [36]. Thus, cardiovascular and metabolic risk factors, subclinical organ damage, such as left-ventricular hypertrophy, and established cardiovascular or renal disease should be sought for in each patient. The current guideline includes abdominal obesity as a factor influencing prognosis. Moreover, the metabolic syndrome is considered an important risk marker with its underlying insulin resistance [36].

The fact that obesity is associated with increased cardiovascular risk received much attention. However, the relationship between obesity and cardiovascular risk is complex. For example, obesity-related risk of death from stroke and cardiovascular disease may be higher in younger than in the older patients [45]. The observation indicates that excess adiposity has deleterious influences on the cardiovascular system already at an early age [12].

Another puzzling observation is that in patients with established cardiovascular disease, overweight and obesity may be protective. The phenomenon is often referred to as the 'obesity paradox'. In a study comparing two different antihypertensive treatment strategies in 22 576 hypertensive patients with coronary artery disease, obese patients responded less in terms of blood pressure reduction. Yet, compared with the normal-weight group, overweight and obese patients were less likely to experience the primary outcome of death, nonfatal myocardial infarction, or nonfatal stroke [46]. A similar analysis was performed in the Systolic Hypertension in the Elderly Program (SHEP) trial data set. This randomized, double-blind, placebo-controlled trial assessed antihypertensive treatment in 4736 men and women aged 60 years or older with isolated systolic hypertension. In the placebo group occurrence of death or stroke was not related to BMI. Treated men and women showed a U-shaped relationship between stroke and mortality and BMI with a nadir of 25.8 kg/m^2 in men and 29.6 /m^2 in women [47]. In contrast, in-hospital mortality following ST-elevation myocardial infarction was higher in patients with BMI greater than 40 kg/m^2 than in less severe obese patients even though acute and chronic treatment was similar and the presentation on admission appeared to be more benign [48]. Overall, the literature suggests that risks associated with arterial hypertension and obesity may not always be additive. How the complex interaction between both risk factors should be handled in clinical risk assessment is not clearly established yet.

BLOOD PRESSURE MEASUREMENTS IN OBESE PATIENTS

Proper blood pressure measurements, which can be challenging in obese patients [49], are tantamount for the diagnosis, risk stratification, and follow-up on treatment. Whereas an in-depth discussion of this issue is beyond the scope of this study and the reader is referred to European guidelines for details [36,50], the following issues ought to be considered. A standardized procedure is recommended for taking office blood pressure starting with a defined

resting period in the seated position in a quiet room. Then repeated measurements should be taken to exclude large variations as a source of wrong blood pressure values. The arm should always be the same. Measurements should be taken at the arm with higher pressure. The cuff should always be positioned at the height of the heart and the arm ought to be supported. No matter which technique is used (office, home, 24-h blood pressure measurement), the use of an appropriately sized cuff is essential. A cuff bladder that is too short and does not appropriately surround the upper arm may result in falsely elevated blood pressure measurements. Measurement of the upper arm circumference can be useful when choosing the proper blood pressure cuff. The following cuff bladder sizes are recommended: upper arm 27–34 cm – cuff bladder 13 × 30 cm; upper arm 35–44 cm – cuff bladder 16 × 38 cm; upper arm 45–52 cm – cuff bladder 20 × 42 cm. Thus, in many obese patients, the regular-size adult blood pressure cuff is not sufficiently large to obtain proper blood pressure measurements.

MANAGEMENT IMPLICATIONS

Following cardiovascular and metabolic risk assessment, a patient presenting with obesity and arterial hypertension requires a carefully considered treatment strategy to attain optimal risk reduction. Because obesity has the potential to raise blood pressure and may add metabolic and cardiovascular risk, the idea that weight loss should be a primary treatment goal is appealing. Moreover, weight loss may improve hypertension-associated organ damage independently of blood pressure. For example, weight loss reduces urinary albumin excretion and left-ventricular mass [51–53]. The ESH/ESC guidelines 2007 propose that weight reduction or weight stabilization should be instituted in overweight patients [36]. The guideline recognizes that the recommendation requires adequate behavioral and expert support but does not provide details of what patients should do to lose weight. The rational for the recommendation is that weight reduction may have a beneficial effect on overall risk and that weight is thought to lower blood pressure. The possibility that weight loss could be detrimental in patients with established cardiovascular disease is not sufficiently addressed. The EASO does not provide specific guidance regarding the management of obese hypertensive patients. Many obese hypertensive patients ultimately require antihypertensive medications. Whereas the underlying pathophysiology of the hypertension may differ between lean and obese patients, current guidelines do not provide specific antihypertensive treatment recommendations for obese patients.

WEIGHT LOSS INFLUENCES ON BLOOD PRESSURE: FACT OR FICTION?

A recent scientific statement by the European Society of Hypertension Working Group on Obesity reviewed the evidence for blood pressure influences of weight loss [54]. Overall, blood pressure reductions attributed to weight loss may be overly optimistic because they are based on short-term weight loss studies. Indeed, blood pressure changes may differ between periods with active weight loss, weight maintenance, and subsequent weight regain. Furthermore, individual blood pressure responses to weight loss are variable given that blood pressure may be 'fat-sensitive' or 'fat-resistant'. Individual blood pressure responses also depend on the actual blood pressure at baseline. Weight loss influences on blood pressure may be modified by a number of concurrent factors including energy balance, dietary composition, physical exercise, comorbidities, genetic profile, and concurrent pharmacological treatments. Finally, in most obesity studies, blood pressure is not the primary outcome measure, and consequently may not have been measured properly.

WEIGHT LOSS THROUGH LIFESTYLE INTERVENTIONS

Lifestyle interventions are the mainstay of obesity management programs and are also advocated in the prevention and treatment of arterial hypertension. Several clinical trials tested long-term influences (≥1 year) on blood pressure [54]. The Trials of Hypertension Prevention are among the largest of such trials, performed in untreated, moderately overweight men and women with high-normal diastolic blood pressure [55–57]. Maximal weight loss of 4.5 kg compared with the usual care group was attained at 6 months and followed by progressive weight regain over 3 years. With weight loss, blood pressure decreased 3.7/2.7 mmHg after 6 months, 1.8/1.3 mmHg after 18 months, and 1.3/0.9 mmHg after 6 years. After 7 years, the intervention effect on body weight had disappeared, whereas a beneficial effect on incident hypertension was still evident. A meta-analysis of 25 randomized controlled trials of nonpharmacological weight loss published between 1966 and 2002 with a total of 4874 participants suggested that on average with each 1 kg body weight reduction, blood pressure decreases by 1.05/0.92 mmHg [58]. Although often suggested by such simple numbers, a linear relationship between the decrease in blood pressure and body weight can neither be assumed for any given starting blood pressure, nor for any given amount of weight loss, as shown by the comparison of dietary and surgical weight loss studies. In the long term, much larger weight reductions may be required to achieve clinically meaningful blood pressure reductions but the benefits may be transitory since few patients are able to maintain weight loss above 3–5% in the long term by lifestyle modification alone. This issue is not addressed in current hypertension guidelines.

WEIGHT LOSS DRUGS

Weight loss medications are not discussed as potential adjunctive treatment in current hypertension guidelines. In a meta-analysis, the intestinal lipase inhibitor orlistat was shown to reduce body weight on average approximately 3 kg compared with placebo [59]. One study compared orlistat and placebo treatment combined with a hypocaloric diet in obese patients with treated but inadequately controlled arterial hypertension. Compared with placebo, orlistat induced an additional 2.7 kg weight loss together with a 2.2 mmHg greater reduction in diastolic blood pressure [60]. The observation is supported by an

analysis of pooled data from five placebo-controlled studies [61].

In a meta-analysis, the norepinephrine and serotonin reuptake inhibitor sibutramine (now withdrawn in Europe) was shown to induce approximately 4.2 kg additional weight loss compared with placebo [59]. When sibutramine treatment was instituted together with an intensive lifestyle intervention, body weight decreased 12 kg over 1 year [62]. The main cardiovascular side effects of sibutramine relate to its inhibition of norepinephrine uptake in peripheral tissues. Sibutramine increases heart rate, particularly in the upright position [63,64]. In some but not all patients, sibutramine increases blood pressure [65,66]. The variable response may be explained by the combination of peripheral norepinephrine uptake inhibition, which tends to raise blood pressure and heart rate, and norepinephrine uptake inhibition in the brain, which reduces centrally generated sympathetic activity through a 'clonidine-like' mechanism [67,68].

Rimonabant, a cannabinoid receptor 1 antagonist (also withdrawn), was tested in a large phase III program in different patient populations (RIO – rimonabant in obesity) [69–72]. Nondiabetic patients treated with rimonabant lost additional 5 kg of body weight compared with placebo. Rimonabant did not interfere with weight loss-induced changes in blood pressure [73]. Developing drugs for weight loss that are both effective and well tolerated has proved extremely challenging, not least because of the increasingly stringent requirements of regulatory authorities that now require that cardiovascular safety be demonstrated in long-term outcome trials. Both sibutramine [74] and rimonabant [75] failed to show cardiovascular benefit, and in high-risk patients taking sibutramine (nonfatal) events were more common despite well sustained weight loss. However, a more recent analysis of the sibutramine outcomes trial showed that the degree of weight loss during the first year of treatment with either sibutramine or placebo was associated with a progressive reduction in risk for primary outcome events and cardiovascular mortality over the 5-year assessment [76]. A responder analysis should be incorporated into the risk benefit analysis of weight loss drugs. In the clinical setting, weight loss drugs are commonly discontinued in nonresponders.

Despite the limited success to achieve long-term weight loss with lifestyle interventions alone, there is still an interest in finding effective and well tolerated weight loss drugs that could also improve blood pressure control. A recent clinical trial tested efficacy and safety of two doses of phentermine and topiramate controlled-release combination as an adjunct to diet and lifestyle modification for weight loss and risk factor. At 56 weeks, body weight changed −1.4 kg with placebo, −8.1 kg with the lower phentermine/topiramate dose, and −10.2 kg with the higher phentermine/topiramate dose. In patients with hypertension, blood pressure decreased by 4.9/3.9 mmHg in the placebo group, 6.9/5.2 mmHg with the lower phentermine/topiramate dose, and 9.1/5.8 mmHg with the higher phentermine/topiramate dose [77]. Whether the beneficial effects on body weight and blood pressure translate into improved cardiovascular outcomes has not yet been reported.

The glucagon-like peptide (GLP)-1 agonist liraglutide in doses of 2.4 and 3.0 mg/day, which are nearly twice the dose used for the treatment of diabetes, has completed phase 2 clinical trials for weight loss in nondiabetic individuals. In a completers analysis, average weight loss of 7.8 kg from baseline was associated with a 12.5 mmHg decrease in systolic blood pressure at 2 years [78]. Between screening and randomization, across all groups, mean systolic blood pressure decreased by 5.7 mmHg, diastolic blood pressure by 3.7 mmHg, and pulse rate fell by 0.9 b.p.m. However, the finding that mean heart rate increased by 3 b.p.m. at 2 years could be a cause for concern.

WEIGHT LOSS THOUGH BARIATRIC SURGERY

Bariatric surgery has been proven effective in reducing body weight in severely obese patients. In an earlier study, gastric bypass surgery led to resolution of arterial hypertension in approximately 70% of the patients after a mean follow-up period of 29 months [79]. In patients with an average BMI of 47 kg/m^2 and documented arterial hypertension, weight loss induced by laparoscopic gastric bypass surgery was associated with a reduction in blood pressure from 140/80 to 120/71 mmHg after 1 year [80]. A recent nonrandomized study in morbidly obese patients with a mean BMI of 45.1 kg/m^2 assessed influences of weight loss through a comprehensive lifestyle intervention or gastric bypass surgery on cardiovascular and metabolic risk markers [81]. Average body weight loss during 12 months follow-up was 10.7 kg in the lifestyle and 41.3 kg in the surgical group. Compared with baseline, office blood pressure decreased 10/6 and 14/12 mmHg in the lifestyle and in the surgical group, respectively [81]. In the hypertensive subgroup, 23% of patients in the lifestyle group and 49% of patients in the surgical group showed remission of arterial hypertension defined as blood pressure less than 140/90 mmHg in the absence of antihypertensive medications. The nonrandomized Swedish Obese Subjects (SOS) study compared patients undergoing bariatric surgery to a well matched conventionally treated control group. After almost 11 years of follow-up, patients in the bariatric surgery group showed sustained reductions in body weight ranging between 14 and 25% depending on the operative procedure and beneficial influences on mortality [82]. Whereas weight reduction elicited a sustained improvement in diabetes risk, there was no long-term effect on the incidence of arterial hypertension [83]. In a subsequent analysis of 10 years of follow-up data, large sustained body weight reductions were required to modestly lower blood pressure [84]. However, in patients in the bariatric surgery group, the adjusted hazard ratio for cardiovascular mortality was significantly reduced to 0.47 compared with the control group [85]. Remarkably, the bariatric surgery group showed a reduced number of fatal strokes (hazard ratio 0.34) after adjustment for baseline differences [85].

ANTIHYPERTENSIVE DRUGS IN OBESE PATIENTS

Since many obese patients do not achieve weight loss or the weight loss is not sufficient to abrogate hypertension in the long term, antihypertensive medications are ultimately

required in most patients. Remarkably, current hypertension guidelines do not provide specific recommendations for the choice of antihypertensive medications in obese patients. Indeed, there are no larger trials addressing the issue [13]. Since a large proportion of hypertensive patients are overweight or obese, data gathered in large clinical trials with hard clinical endpoints, which is the foundation of the ESH Guidelines, are at least in part applicable [36]. The guideline proposes a flexible approach to hypertensive patients taking into consideration associated risk factors, such as presence of the metabolic syndrome, as well as organ damage or cardiovascular disease. However, to address the specific needs of obese patients, these recommendations have to be modified on the basis of few existing data and our current understanding of the mechanisms involved in obesity-associated arterial hypertension.

Given the volume expansion and the neurohumoral activation in obesity-associated arterial hypertension, diuretics, renin-angiotensin system inhibitors, and beta-blockers are reasonable first choices. However, when choosing antihypertensive medications metabolic side effects should be taken into consideration. Inhibitors of the renin-angiotensin-system are considered first-line antihypertensives for most patients. Because of their broad spectrum of beneficial effects, angiotensin-converting enzyme inhibitors are currently considered to be the most appropriate drug for antihypertensive treatment of obese patients. Angiotensin receptor blockers can be utilized in patients who do not tolerate angiotensin-converting enzyme inhibition. The Diabetes REduction Assessment with ramipril and rosiglitazone Medication study suggested that the reduction in diabetes risk with angiotensin-converting enzyme inhibition in patients with low cardiovascular risk may not be as pronounced as expected [86], but that study did not target an obese hypertensive population. Cleary, renin-angiotensin system blockade in patients with obesity-related hypertension is unlikely to worsen glucose or lipid metabolism.

Beta-blockers reduce cardiac output and renin activity, both of which are frequently increased in obese patients. It is therefore not surprising that beta-blockers alone [87], or in combination with alpha-adrenoreceptor blockers [6], were more effective in decreasing blood pressure in obese than in lean hypertensive individuals. Limitations for the use of beta-blockers, especially in young obese hypertensive patients without cardiac and renal complications, are related to their potential negative effects on glucose metabolism and body weight [88,89]. Beta-blockers with vasodilating properties, such as carvedilol, may be less likely to worsen glucose metabolism [90]. A prospective and retrospective analysis of the Carvedilol or Metoprolol European Trial (COMET) assessed the development of new-onset diabetes mellitus in chronic heart failure patients. Diabetic events were less likely to occur in carvedilol compared with metoprolol-treated patients (hazard ratio 0.78) [91].

Diuretic agents could be used with respect to the well described hypervolemia and sodium retention in obesity. Combination of low-dose thiazide diuretics with renin–angiotensin system blockers may reduce hyperkalemia risk while improving blood pressure control. A recently conducted analysis started a controversy regarding the choice of diuretic in the treatment of arterial hypertension. The authors suggested that in contrast, to other thiazide-type diuretics, typically applied hydrochorothiazide doses of 12.5–25 mg/day have never been shown to reduce hard cardiovascular endpoints [92]. However, the conclusion has been challenged by others [93]. Consideration should be given to the impairment of insulin sensitivity and deterioration of glucose metabolism that could be caused by high-dose thiazide diuretics. Overall, thiazide diuretics may not be the first choice for most obese hypertensive patients. However, in patients not responding to monotherapy, thiazide diuretics are a reasonable second or third antihypertensive drug.

Dihydropyridine calcium channel blockers are effective in lowering blood pressure. One study suggested a blunted response in obese hypertensive patients to isradipine [88], whereas another study with amlodipine did not confirm this finding [94]. The recent Avoiding Cardiovascular events through COMbination therapy in Patients LIiving with Systolic Hypertension trial trial compared combination therapies amlodipine/benazepril vs. hydrochlorothiazide/benazepril in a hypertensive patient population with a considerable number of obese patients (mean BMI 31.0 kg/m^2 in both groups) [95]. The trial was terminated early due to reduced cardiovascular mortality with the amlodipine/benazepril combination. The observation that obese patients are more likely to experience peripheral edema with dihydropyridine calcium channel blocker treatment compared with lean patients is a potential limitation.

Even though renin–angiotensin system inhibitors may be the first choice for most obese hypertensive patients, antihypertensive monotherapy is seldom sufficient to control blood pressure. In the primary care setting, more than half of the obese hypertensive patients are treated with two or more antihypertensive drugs [1].

TREATMENT OF RESISTANT HYPERTENSION IN OBESE PATIENTS

Data on how to treat obese patients with resistant arterial hypertension are scarce. A recent study suggests that in these patients, adding the mineralocorticoid antagonist spironolactone may be useful. In patients with true resistant hypertension diagnosed by ambulatory blood pressure monitoring, spironolactone treatment in doses of 25–100 mg/day was started [96]. A second ambulatory blood pressure monitoring performed after a median interval of 7 months showed a 16/9 mmHg reduction in blood pressure. Remarkably, higher waist circumference was associated with better response to spironolactone. These findings point to the special role of aldosterone in obesity-associated hypertension. Direct renin inhibition may be an effective alternative treatment approach in obese hypertensive patients [94,97]. However, the medication should be used with caution, particularly in combination with other renin–angiotensin system inhibitors or renal disease. Recently, a large outcomes study testing aliskiren in combination with either angiotensin receptor blockade or angiotensin-converting enzyme inhibition in high-risk patients with diabetes mellitus [98] was prematurely

discontinued due to increased severe adverse events. Given the important role of the sympathetic nervous system in the pathogenesis of obesity-associated arterial hypertension and insulin resistance, central sympatholytic drugs are another treatment option for patients not responding to or not tolerating first-line antihypertensive drugs [99].

Devices for treatment of resistant arterial hypertension have recently undergone clinical testing. Many of the patients included in these trials were overweight or obese. Renal sympathetic denervation through a novel catheter-based approach substantially reduced blood pressure in patients with treatment-resistant arterial hypertension with an average BMI of 31 kg/m^2 [100]. The response may be mediated in part through ablation of renal afferent nerves decreasing centrally generated sympathetic activity [101]. Renal sympathetic denervation may also improve glucose metabolism [102]. Another device-based approach is electrical baroreflex activation. The treatment requires surgical implantation of a pacemaker device and electrodes located at the level of the carotid sinus. Baroreflex activation therapy reduces blood pressure through sympathetic inhibition [103,104]. In a recent controlled clinical trial including treatment-resistant hypertensive patients with an average BMI of 32.4 kg/m^2, baroreflex activation therapy did not increase the proportion of patients achieving an at least 10 mmHg reduction in systolic blood pressure at month 6 (primary endpoint) [105]. However, the treatment increased the likelihood of achieving blood pressure control and showed promising effects on long-term blood pressure control. Clearly, both treatments need to be tested in larger clinical trials with hard endpoints.

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Conflicts of interest

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