THE ASSOCIATION BETWEEN ANTIHYPERTENSIVE USE AND BLOOD PRESSURE IS INFLUENCED BY OBESITY

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ABSTRACT

We examined whether blood pressure (BP) attained when using various antihypertensive medications differs by body mass index (BMI) and if antihypertensive medication use is associated with differences in other metabolic risk factors, independent of BMI. Individuals with hypertension from the National Health and Nutrition Examination Survey (NHANES) from 1999-2014 were used (n=15,285) to examine the main effects and interaction between antihypertensive use and BMI. Generally, antihypertensive users had lower BP than those taking no BP medications (NoBPMed) (P<0.05), whereby in women, the differences in systolic BP between angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) users and NoBPMed was greater in those with obesity compared to normal weight women (P<0.05). Diastolic BP differences between women ARB users and NoBPMed were also greatest in obesity (P<0.05) whilst there were no differences in normal weight individuals (P>0.05). Furthermore, glucose levels, and waist circumference (in women) were higher in those using ACE inhibitors compared to diuretics (P<0.05). ACE inhibitors and ARBs may be more beneficial for BP reduction in women with obesity. However, potential cardiometabolic side effects of antihypertensive medications should also be considered.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACE	Angiotensin-Converting Enzyme
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
CCB	Calcium Channel Blocker
CO	Cardiac Output
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
FPG	Fasting Plasma Glucose
HDL	High Density Lipoprotein
NHANES	National Health and Nutrition Examination Survey
RAAS	Renin-Angiotensin-Aldosterone System
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
TG	Triglyceride
WC	Waist Circumference

1.0 GENERAL INTRODUCTION

Obesity is becoming a global epidemic as its prevalence is increasing at an alarming rate around the world (1,2). Worldwide obesity has nearly tripled since 1975 and as of 2016, estimates show that over 650 million adults are living with obesity (3). Obesity has many associated cardiovascular and metabolic disorders that have become a major threat to public health (4). It is well established that obesity is a major risk factor for hypertension, which contributes to the development and progression of cardiovascular disease (CVD), the leading cause of mortality worldwide (3,5,6). Although lifestyle modifications are important in obesity-associated hypertension management, most individuals with hypertension require antihypertensive medications to reduce blood pressure (BP) and maintain it within acceptable ranges (7).

Research has shown that individuals with obesity are more likely to use antihypertensive medications to treat hypertension (8). With the shift of hypertension treatment towards pharmacological agents and the role obesity plays in the pathogenesis of hypertension (9), further research is necessary to examine the association between antihypertensive medication use and obesity on BP for this population. Given that hypertension is often accompanied with type 2 diabetes and metabolic syndrome, antihypertensive medications may or may not exacerbate the health risks associated with these conditions (10). Therefore, the aim of the present thesis is to determine if BP attained using various antihypertensive medications differs by body mass index (BMI) and to determine if the use of these antihypertensive medications is associated with differences in glucose and lipid levels, and waist circumference, independent of BMI. The findings from this study may have important clinical implications for clinicians and health care

professionals by providing a greater understanding on whether antihypertensive medications are more or less beneficial for individuals with hypertension and obesity.

2.0 REVIEW OF RELATED LITERATURE

Introduction

It is currently estimated that one in three US adults is living with obesity or hypertension (11,12). With these epidemic proportions, it is important to understand the pathways involved in regulating blood pressure, how antihypertensive medications act to lower blood pressure (BP), and how obesity alters these relationships.

The following review will discuss hypertension, the regulation of normal blood pressure, obesity, health risks associated with obesity, physiological alterations that result in high blood pressure, and specifically how high blood pressure develops in those individuals with obesity. The review will also describe the current interventions available to manage and treat hypertension including pharmacotherapy in those with obesity. Lastly, the review will discuss medication dosing strategies unique for individuals with obesity.

Hypertension

Hypertension is a condition in which the blood vessels have consistently raised blood pressure (13). Normal adults have a systolic/diastolic blood pressure (SBP/DBP) reading of 120/80 mmHg or less and above 90/60 mmHg. When the blood pressure is greater than 140/90 mmHg, blood pressure is considered to be within the hypertensive range (14). Most individuals with hypertension have no other symptoms, and therefore hypertension is considered to be a silent killer and significantly increases the risk of cardiovascular disease (CVD) (13).

Regulation of Blood Pressure

The regulation of blood pressure is a very complex physiologic function, dependent on the actions of the cardiovascular, neural, renal, and endocrine systems (15). Blood pressure may rise or fall depending on the physiological circumstances and metabolic demands from the body (16). Therefore, in investigating the pathophysiology of hypertension, a good understanding of the factors responsible for normal blood pressure control is needed (15,17,18).

The blood pressure regulation system functions to correct deviations from the setpoint value (17). Overall, the system works using sensors that respond to blood pressure, evaluators that compare the existing blood pressure to the setpoint, and effector mechanisms that bring about changes in cardiac output (CO) and peripheral vascular resistance to reduce the difference between the blood pressure and setpoint (17,18). The mechanisms used to regulate blood pressure depend on whether short-term or long-term adaptation is needed (18).

Short-Term Regulation

One of the main mechanisms behind short-term regulation of blood pressure is the baroreceptor reflex mechanism (**Appendix A**). Baroreceptors are pressure-sensitive sensors located in the walls of the blood vessels and heart that respond to blood pressure changes by sending impulses to the brain causing changes in heart rate and smooth muscle tone (18). Under normal physiological conditions, the baroreceptor reflex adjusts the level of sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) activation to allow maintenance of a constant arterial pressure by use of a negative feedback homeostatic system (19). When blood pressure drops too low, baroreceptor firing is reduced in order to increase blood pressure through vasoconstriction and increased cardiac output by increased sympathetic stimulation via norepinephrine (NE) release and reduced parasympathetic stimulation via

acetylcholine (ACh) reuptake (20). When blood pressure rises too high, baroreceptor firing is enhanced in order to lower blood pressure through reduced vasoconstriction and decreased cardiac output by decreased sympathetic stimulation via NE reuptake and increased parasympathetic stimulation via ACh release (21,22).

Sympathetic Nervous System (SNS)

The stimulated effects of the sympathetic nervous system (SNS) is achieved when catecholamines like epinephrine and norepinephrine bind to specific receptors known as adrenergic receptors (23). β-adrenergic receptors are found in the heart, blood vessels, kidneys, and the lungs, and are responsible for regulating heart rate and blood pressure. There are two β-adrenergic receptors responsible for blood pressure regulation, the β-1 and β-2 receptor. β-1 adrenergic receptors are located predominantly in the heart, while β-2 adrenergic receptors are located in the blood vessels and other organs (24). Therefore, when bound by norepinephrine, β-1 receptors increase CO, which increases blood pressure, and when bound by epinephrine, β-2 receptors increase vascular smooth muscle relaxation; which decreases blood pressure. Combined, there is balanced blood pressure regulation.

The Renin-Angiotensin-Aldosterone System

RAAS is a key regulator of blood pressure and fluid balance in the body (**Appendix B**). When sodium levels in the body are low, or blood potassium is high, the kidney secretes renin. Renin converts angiotensinogen, which is secreted by the liver, to angiotensin I which is then converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE). Angiotensin II is a vasoconstrictor that acts on blood vessels and also promotes aldosterone secretion, both of

which lead to water and salt retention, and potassium excretion. Additionally, angiotensin II causes vasoconstriction through increased SNS activity as a secondary effect which further helps to restore the balance of sodium, potassium, and water (25).

Long-Term Regulation

Although the neural and hormonal mechanisms which act to control blood pressure act rapidly, they are not effective in controlling blood pressure over days, weeks, or months (17,26). Instead, the brain and kidneys work together to control long-term blood pressure by regulating the secretion of water and sodium (18). In the situation where RAAS is inappropriately active, blood pressure is increased via water and sodium retention by angiotensin II (27). When the body has excess extracellular fluids (increased sodium and water), the rate at which water and salt is excreted (diuresis and natriuresis, respectively) is increased (17). In hypertension, there is a chronically higher release of vasoconstrictor substances and increased renal SNS activity (17,18,28). Accordingly, this may shift the diuresis-natriuresis process to a higher fluid and blood pressure setpoint level. Therefore, many antihypertensive medications act on the diuresis-natriuresis process by increasing sodium and water elimination to treat chronic hypertension (17,29).

Obesity

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to an individual's health (30). A commonly used measure in classifying overweight and obesity in the adult population is body mass index (BMI). BMI represents an index of an individual's size that is calculated by dividing an individual's weight in kilograms by the height in metres squared (kg/m^2). BMI can be classified into four categories; underweight, normal weight, overweight, and obesity. Underweight is defined as a BMI < 18.5 kg/m^2. Normal weight is defined as a BMI

≥ 18.5 kg/m^2 and BMI < 25 kg/m^2. Overweight is defined as BMI ≥ 25 kg/m^2 and BMI < 30 kg/m^2. Lastly, obesity is defined as a BMI ≥ 30 kg/m^2 (31). BMI provides a crude population-level measure of overweight and obesity (30,32).

Obesity Related Health Risks

Obesity has increased steadily over the years and has become a major public health issue (33,34). Worldwide, over 1.9 billion adults are overweight or are living with obesity (30). In the United States, more than 67% of adults are overweight or are living with obesity (35). This is of concern as those with obesity are at increased risk of morbidity and mortality from a number of chronic diseases including hypertension, type 2 diabetes, dyslipidemia, cancer, and CVD (36–38).

Obesity and Hypertension

The effects of obesity on hypertension have long been recognized (9). Studies that have examined the link between BMI and blood pressure have reported that a 5% weight gain is associated with a 20-30% increase in hypertension incidence (39). It is also estimated that at least 60% of incident hypertension is directly associated with obesity, and the combination of obesity and hypertension is recognized as a leading cause of CVD risk (9,39,40).

The etiology of hypertension differs widely amongst individuals with obesity (41). There is not one mechanism whereby obesity causes hypertension (42). Studies have shown that a variety of mechanisms involving SNS, RAAS, and diuresis-natriuresis may be altered in obesity (43). Therefore, a review of these changes would add to our understanding of obesity-associated hypertension (41,43,44).

SNS activity is greatly enhanced in those with concurrent obesity and hypertension (45). As mentioned before, in hypertension there is increased renal SNS activity, leading to over-secretion of renin (25). Additionally, adipocytes have been shown to secrete angiotensinogen (46,47). Coupled together, these processes lead to upregulation of RAAS resulting in consistent high blood pressure.

Angiotensin II has also been shown to play an indirect role in obesity-associated hypertension. Angiotensin II may influence adipocyte growth and differentiation (48,49). Furthermore, angiotensin II may directly stimulate leptin release from adipocytes, which can cause increased SNS activity (49). In severe obesity, there are chronic increases in leptin and can therefore have substantial effects of increased SNS activity and blood pressure (50). Elevated aldosterone levels are also observed in individuals with obesity-associated hypertension, especially in those with visceral obesity (51), however the exact mechanisms by which excess fat could increase aldosterone are still unknown.

Management of Hypertension in Obesity

There are many different therapies available for managing hypertension in obesity. These therapies can be lifestyle interventions and pharmacological therapies (52). Lifestyle interventions are usually recommended as the initial treatment strategy in lowering blood pressure which include limiting sodium intake and alcohol consumption, weight loss, and increasing physical activity. (53).

Diet

Dietary modifications which are associated with effective reductions in blood pressure include reduced salt intake, increased potassium intake, moderation of reduced alcohol consumption, and consumption of a healthy diet, such as the Dietary Approaches to Stop Hypertension (DASH) diet (54). The DASH diet encourages individuals at risk of or with hypertension to eat foods that are rich in protein, fiber, potassium, magnesium, and calcium. These foods include fruits and vegetables, beans, nuts, whole grains, and low-fat dairy products (55). The combination of these foods along with limited high fat, sodium, and sugar products have been shown to lower blood pressure (53,56,57). The DASH diet is also a good choice for weight management particularly for weight reduction in those with overweight and obesity to reduce the risk of CVD (58). It has been suggested that every kilogram of weight reduction is associated with a 1 mmHg decrease in SBP and DBP (59). However, data from the National Health and Nutrition Examination Survey (NHANES) in the US from 1988 to 1994 and 1999 to 2004 stated that less than 20% of adults with known hypertension were classified as accordant with the DASH diet (55,60,61). Therefore, while the DASH diet shows evidence as an effective form of hypertension treatment, there is a low adoption of the diet.

Physical Activity

Low physical activity is a major risk factor for hypertension (62). Therefore, physical activity is recommended for the prevention and treatment for hypertension (63). Exercise training is an important initial step that is highly efficacious in the treatment of individuals with mild hypertension, with or without weight loss (64). Across many studies, aerobic and resistance training at moderate intensity has been shown to decrease blood pressure through reductions in vascular resistance, with average SBP and DBP reductions of 8 mmHg and 4 mmHg, respectively (62,65). Additionally, acute improvements in blood pressure have been observed

after a single exercise session and can last up to 16 hours even with low-intensity exercise (66). There is a modest dose-response relationship between physical activity and blood pressure. Studies have observed that even 30-60 min of exercise per week is sufficient to reduce both SBP and DBP in hypertensive individuals (67). The magnitude of SBP reduction is also greater in hypertensive individuals that exercise 60-90 min per week. However, there are no greater reductions in blood pressure beyond 90 minutes of physical activity per week. Therefore, reductions in blood pressure can be achieved with minimal amounts of exercise.

Studies suggest that physical activity programs with weight loss provide beneficial effects in CVD risk reduction (68). Exercise along with weight loss can have SBP reductions of 13 mmHg and 8 mmHg for DBP (69). However, when looking at long-term adherence, about 50% of adults who start a physical activity program drop out within a few months (70). Thus, it may not be surprising that the prevalence of individuals meeting physical activity guidelines is only one in five USA adults (71).

Antihypertensive Medications

In the United States, >90% of diagnosed hypertension is treated with lifestyle interventions and medication use. However, to achieve optimum blood pressure goals, factors including access, time commitment, compliance and financial barriers may affect the delivery of these lifestyle interventions (70). Therefore, it may not be surprising that ~65% of patients use pharmacological blood pressure treatments (72). Antihypertensive pharmacotherapy has been demonstrated to significantly reduce the risk of death from stroke and CVD by approximately 11% (73). Therefore, individuals with hypertension that cannot achieve blood pressure reductions with lifestyle interventions are recommended to add pharmacological therapy in the treatment of hypertension.

Medications available for treatment of Hypertension

Currently, there are five major first-line antihypertensive drug classes available; diuretics, ACE inhibitors, angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and β-blockers that have differing underlying mechanisms (74,75).

Diuretics

Diuretics are the most common antihypertensive medication prescribed (76,77). Also called "water pills," the major role of diuretics is to reduce sodium reabsorption in the kidney and increase urine excretion (76,78). As mentioned previously, in hypertension the diuresis-natriuresis curve is shifted to a high pressure level, therefore diuretics work by increasing urinary sodium excretion and water loss to decrease blood pressure. Currently, there are three main types of diuretics: loop diuretics, thiazide diuretics, and potassium-sparing diuretics. Loop and thiazide diuretics impair sodium reabsorption by blocking the sodium transporters in the ascending loop of Henle and the distal convoluted tubule, respectively (79). Potassium-sparing diuretics work in the collecting duct and either work as aldosterone antagonists or by inhibition of sodium transporters (80). Potassium-sparing diuretics are usually prescribed when potassium levels are low or are depleted due to other medications taken (81). Current guidelines by the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend that for uncomplicated hypertension, thiazide-diuretics should be used, either alone or combined with drugs from other classes (74).

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors and ARBs are also first-line antihypertensive agents that have important roles that modify the RAAS mechanisms that control blood pressure (82). ACE inhibitors decrease the production of angiotensin II by inhibiting its conversion from angiotensin I, while ARBs decrease the effects of angiotensin II by selectively blocking the type I receptor (AT1) of angiotensin II (83). Therefore, both drugs act on angiotensin II activity, while ARBs may offer more complete angiotensin II inhibition than ACE inhibitors due to selective blockade of the receptor site (84). ACE inhibitors also decrease blood pressure by preventing the breakdown of bradykinin, resulting in vasodilation and increased blood flow to tissues (85). ARBs are associated with fewer side effects and higher rates of adherence as compared to ACE inhibitors (86). However, there is more available research on the use of ACE inhibitors in CVD risk reduction that may be considered before choosing ARBs over ACE inhibitors.

β-Blockers

β-blockers are agents that play an important role in the regulation of blood pressure and heart function (87). β-blockers are competitive antagonists that bind to beta adrenergic receptors (88). In the kidneys, NE binding to the receptors induces renin secretion leading to activation of RAAS and increased blood pressure by angiotensin II and aldosterone secretion. Therefore, β-blockers work to inhibit these pathways resulting in lower blood pressure (89). However, β-blockers can be selective or non-selective. Although there is no difference in BP lowering between β-1-selective and nonselective β-blockers (β-1 and β-2), nonselective beta blockers over time may impair renal function by reduction in glomerular filtration rate (90,91). Therefore, β-1-selective blockers may be more appropriate in the treatment of hypertension.

Calcium Channel Blockers

CCBs have been widely used to treat hypertension and are effective in reducing blood pressure levels along with reducing CVD risks associated with hypertension. They have good tolerability with few side effects (92). CCBs play a role in the inhibition of voltage-gated calcium channels in the vascular smooth muscle (93). CCBs decrease systemic vascular resistance and lower arterial blood pressure by causing vascular smooth muscle relaxation (94). However, at high doses, CCBs can in fact increase RAAS activity as well (95,96). Therefore, CCBs must be carefully prescribed and/or combined with other antihypertensive medications.

Antihypertensive Therapy in Obesity

In those with obesity, antihypertensive drug therapy must be administered carefully to obtain optimal blood pressure and CVD risk reduction (97). In the primary care setting, antihypertensive therapy is considered in individuals with BMI $\geq$ 30 kg/m^2 or with other comorbidities such as type 2 diabetes and dyslipidemia present. Those with obesity are reported to require more medications to achieve similar blood pressure values than those who are normal weight (98). As mentioned previously, angiotensinogen is overly expressed in obesity, therefore ACE inhibitors and ARBs are often used in patients with obesity (97,99–101). Additionally, ACE inhibitors/ARBs may have the advantage of reducing the risk of new onset diabetes, while β-blockers and thiazide diuretics may in fact increase the risk of diabetes (100,102). Another point for consideration in patients with obesity is that the use of β-blockers is associated with a 10% lower metabolic rate which may lead to weight gain or impair weight loss attempts (103). Diuretics appear to have dose-related effects in regard to the risk of dyslipidemia and insulin resistance, therefore low dose diuretics are recommended if used as an adjunct (104). CCBs have also been proven to be as effective as ACE inhibitors or ARBs and have not been associated with

weight gain or adverse changes in lipids. (105). Thus, with a wide variety of antihypertensive medications available, it is unclear whether hypertensive individuals with obesity using these medications have differing blood pressures than those who are normal weight or overweight.

Medication Dosing in Obesity

While many agents are available to treat various conditions associated with obesity, knowledge regarding how they work in obesity is limited (106,107). In obesity, there are changes in hepatic metabolism and renal excretion that affect pharmacokinetics (108,109). Pharmacokinetic studies show that in obesity, lipophilic drugs tend to be absorbed by adipose tissue quickly and hydrophilic drugs that are eliminated by renal excretion have increased clearance from the body, which can lead to overdose or underdose situations (106,110,111). Therefore, in order to ensure adequate drug concentrations in those with obesity, drug treatment must be carefully monitored and dose testing in populations with obesity.

Summary of Literature

It is well understood that there has been a substantial rise in hypertension and obesity. There is clearly a link between obesity and hypertension, and when combined, there is an even considerably higher risk of CVD. There has also been a rise in individuals with hypertension and obesity using these medications. Therefore, with the increased use of pharmacological agents to treat hypertension, further research is necessary to examine the association between antihypertensive medication use and obesity on blood pressure for this population.
The findings from this study may have important clinical significance for health care professionals by providing a greater understanding on whether blood pressure attained using

various antihypertensive medications differ by BMI classes. These findings may also assist health care professionals on whether certain antihypertensive medications may be more or less beneficial for populations with obesity.

3.0 MANUSCRIPT

Abstract

Aim: We examined whether blood pressure (BP) attained when using various antihypertensive medications differs by body mass index (BMI) and if antihypertensive medication use is associated with differences in other metabolic risk factors, independent of BMI.

Methods: Individuals with hypertension from the National Health and Nutrition Examination Survey (NHANES) from 1999-2014 were used (n=15,285). Linear regression analyses were used to examine the main effects and interaction between antihypertensive use and BMI.

Results: Generally, antihypertensive users had lower BP than those taking no BP medications (NoBPMed) (P<0.05), whereby in women, the differences in systolic BP between angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) users and NoBPMed was greater in those with obesity (ACE inhibitors: -14 ± 1 mmHg, ARB: -16 ± 1 mmHg) compared to normal weight individuals (ACE inhibitors: -9 ± 1 mmHg, ARB: -11 ± 1 mmHg) (P<0.05). Diastolic BP differences between women ARB users and NoBPMed were also greatest in obesity (-5 ± 1 mmHg) (P<0.05) whilst there were no differences in normal weight individuals (-1 ± 1 mmHg) (P>0.05). Furthermore, glucose levels, and waist circumference in women were higher in those using ACE inhibitors compared to diuretics (P<0.05).

Conclusion: ACE inhibitors and ARBs may be more beneficial for BP reduction in women with obesity, with no obesity-related differences for antihypertensive medication in men. However, potential cardiometabolic side effects of antihypertensive medications should be considered.

Introduction

Cardiovascular disease (CVD) is now recognized as the leading cause of death worldwide (112). In 2013, more than 50 million deaths were reported globally, and 32% of these deaths were attributable to CVD. Hypertension is the most quantitatively important risk factor for premature CVD, accounting for an estimated 54% of all strokes and 47% of all ischemic heart disease events globally, and is more common than other CVD risk factors such as dyslipidemia and type 2 diabetes (113). Obesity is a risk factor for hypertension (114,115), and over the past few decades, the rates of obesity have risen dramatically (116). Considering the independent and combined CVD risks of obesity and hypertension (117), these chronic conditions are major public health issues.

The prevalence of antihypertensive medication use in US adults with hypertension has risen from 64% to 77% in 2001 to 2010 (72). Overall, the use of first-line antihypertensive medications including thiazide diuretics, β-blockers, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has increased by 23%, 57%, 31%, and 100%, respectively from 2001 to 2010 (72). However, there are many differences in the physiology of obesity-related hypertension that may impact the effectiveness of antihypertensive medications in populations with varying obesity. Moreover, body compositional differences have been reported to influence the pharmacokinetics of various medications (118,119). Further, individuals with obesity are reported to be less adherent to taking medications than lean individuals (120). It is also well known that medication adherence in clinical trials are far superior to real-world settings (121,122). Thus, with the substantial rise in antihypertensive medication use combined with the high obesity prevalence, it is important to examine whether

there are medication-related blood pressure differences by obesity status in a United States nationally representative sample.

There are few studies that have directly compared blood pressure differences in antihypertensive users across different body mass index (BMI) categories (123–125). The INVEST (International Verapamil SR-Trandolapril) trial and a post-hoc analysis of the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial in particular, found that individuals with obesity on calcium channel blockers (CCBs) and diuretics in combination with ACE inhibitors were at lower risk for experiencing a cardiovascular event than their lean counterparts (123,124). To date, no studies have compared blood pressure differences between different BMIs for all of the common first-line antihypertensive classes (122–125). Further, past literature has only examined the individual blood pressure effects of the antihypertensive classes in combination (124–127), and thus the individual medication effects becomes difficult to assess. In addition, none of these studies observed the association between antihypertensive medication use on other metabolic risk factors. Therefore, the objective of this study will be to determine if blood pressure attained using various antihypertensive medications differs by BMI. This study will also determine if the use of antihypertensive medications is associated with differences in glucose and lipid levels, and waist circumference independent of BMI.

Methods

Participants

The National Health and Nutrition Examination Survey (NHANES) is a series of health surveys conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). NHANES utilizes a cross-sectional, multistage, probability study design to select participants that are nationally representative of the civilian, non-institutionalized U.S. population by oversampling African Americans, Mexican Americans, and individuals aged 60 years or older (128). The survey consists of an in-home interview, followed by a standardized health examination and laboratory tests in mobile examination centers (MEC). All participants provided their informed written consent for the in-home interview and physical examination, and ethics were approved by the NCHS Research Ethics Review Board. Further information on the study protocol and design is reported by CDC (129).

NHANES continuous data (1999-2014) were used (n=82,091). Participants were excluded from analysis if they were under the age of 18 years old (n=34,735), if they had a BMI< 18.5 kg/m^2 (n=653), and if they answered "Yes" to "Are you now taking prescribed medicine for high blood pressure?" but had no blood pressure medication data (n=588). Additionally, participants were excluded if they had missing data for BMI (n=3,246), health insurance status (n=347), smoking status (n=3,067), physical activity (n=5), education (n=104), systolic blood pressure (SBP; n=4,380), and diastolic blood pressure (DBP; n=4,611). The final sample size was 37,763 of which 15,285 were hypertensive (defined as self-reported doctor-diagnosed hypertension or SBP ≥140 mmHg or DBP ≥90 mmHg or self-reported antihypertensive medication use) and used for analysis.

Any additional missing data for analysis of fasting plasma glucose (FPG), waist circumference (WC), triglyceride (TG), and high-density lipoprotein (HDL) was excluded (FPG: n=20,177; WC: n=1,061; TG: n=20,325; HDL: n=1,969). The final sample size for analysis was 7,146 for FPG, 14,691 for WC, and 6,731 for HDL and TGs.

Survey Methods

Household Questionnaires

Age, sex (male/female), ethnicity (white/other), health insurance status (insured/uninsured), education status (< high school/ ≥ high school), physical activity (active/inactive) and smoking status (smoker/non-smoker) were assessed through household questionnaires. Participants were considered insured if they answered "Yes" to, "Are you covered by health insurance or some kind of health care plan? (including employment, private, and government health care plans)." Participants who answered "Yes" to performing moderate or vigorous physical activity leading to small or large increases in breathing and heart rate for at least 10 minutes continuously in the past 30 days were considered active. Participants that were current smokers were coded as smokers.

Examination Measures

All body measures were obtained by trained health technicians. Standing height was measured to the nearest tenth of a centimeter (0.1 cm) using a stadiometer with a fixed vertical backboard and an adjustable head piece. Weight was measured in kilograms using a digital weight scale. BMI was then calculated using weight in kilograms divided by height in meters squared (kg/m^2). Participants were categorized as normal weight ($18.5\ kg/m^2 \leq BMI < 25\ kg/m^2$), overweight ($25\ kg/m^2 \leq BMI < 30\ kg/m^2$), or obesity ($BMI \geq 30\ kg/m^2$). FPG and TG levels were

assessed on participants who were examined in the morning session after a minimum eight hours fast (NHANES 1999-2004) or nine hours fast (NHANES 2005-2014).

Blood pressure measurements were obtained using a manual mercury sphygmomanometer. The blood pressure cuff was placed on the right arm unless a specific condition was reported prohibiting use of the right arm. Participants were seated for 5 minutes and were told to rest quietly before beginning blood pressure measurements. At minimum, three measurements were recorded with 30 seconds rest in between each measurement. If necessary, a fourth measurement was recorded. Blood pressure measurements were averaged and used for analysis.

Prescription Medication Use

Prescription medication information was obtained through household questionnaires. Participants who had used prescription medication in the past 30 days were asked to provide the name of the medication and if possible, to provide the medication container to the examiner. NHANES uses a prescription medication database, Lexicon Plus®, that sorts medications by drug ingredients and therapeutic categories. Blood pressure medications were categorized as ACE inhibitors (n=4,609), β-blockers (n=4,243), diuretics (n=5,054), CCBs (n=3,387), ARBs (n=2,279), and Other (alpha blockers, renin inhibitors, and vasodilators, n=974). Combination therapy was considered if participants were using ≥2 different types of antihypertensive medications. Monotherapy was considered if participants were using only one (1) type of antihypertensive medication. The no BP drug group (NoBPMed) included individuals that were hypertensive but not taking antihypertensive medications (n=5,443).

Statistical Analysis

Descriptive characteristics were stratified by antihypertensive medication drug type. All analyses of antihypertensive drug types were compared to NoBPMed (hypertensive adults without reported antihypertensive medication use). Data was presented as means (SE) or prevalence, % (SE). The differences between sample characteristics were evaluated using one-way analysis of variance (ANOVA) with Tukey's post hoc tests for continuous variables, and chi-square tests for categorical variables. Linear regression analyses were used to assess the individual and joint associations of BMI category and antihypertensive medication use on blood pressure adjusted for age, sex, ethnicity, education, health insurance status, physical activity, smoking status, and number of antihypertensive medications. Predicted least squared mean BP was computed for each BMI category-antihypertensive use group. Predicted least squared means were computed for FPG, WC, TG, and HDL levels adjusted for age, sex, BMI, ethnicity, education, health insurance status, physical activity, smoking status. FPG analysis was further adjusted for type 2 diabetes. Differences were evaluated using Tukey's multiple comparison tests.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and weighted to be representative of the U.S. population. Hypothesis testing was performed at a significance level, $\alpha = 0.05$.

Results

Participant Characteristics

Participant characteristics are shown in **Table 1**. Individuals using antihypertensive medication were older, were more likely to have health insurance and obesity, and were less likely to smoke and be physically active than individuals not using antihypertensives ($P < 0.05$). Individuals taking antihypertensive medication had significantly lower systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to NoBPMed ($P < 0.0001$). Similar results were observed following adjustment for age, sex, BMI, ethnicity, education, smoking, physical activity, health insurance, and number of antihypertensive medications (data not shown). With a therapeutic goal of <140/90 mmHg, the blood pressure control rate for overall antihypertensive users was 68.4%, where individuals with obesity were more likely to have controlled blood pressure, compared to normal weight users (70.4% vs. 63.3%, OR, 95% CI: 1.4, 1.2-1.6).

Association between BMI category and antihypertensive medication use

There was no interaction effect observed between BMI category and β-blocker, CCB, or Other antihypertensive use on SBP and DBP (**Figure 1**, $P > 0.05$). However, there was a significant interaction between antihypertensive medication use and BMI category on DBP in those using diuretics ($P = 0.0414$). The difference in DBP between diuretic users and NoBPMed was slightly greater in those with obesity (-2 ± 1 mmHg) compared to those with overweight, although minimal (-1 ± 1 mmHg, $P = 0.0198$). Diuretic users had no significant differences in SBP by BMI category ($P < 0.05$).

There were significant interaction effects between ACE inhibitor or ARB use and BMI by sex on BP (**Figure 2**, ACE inhibitors SBP: $P = 0.0035$; ARB SBP: $P = 0.0129$; ARB DBP: P

= 0.0015). In women, the difference in SBP between ACE inhibitor users and NoBPMed was significantly greater in those with obesity (-14 ± 1 mmHg, *P* = 0.0004) and overweight (-14 ± 1 mmHg, *P* = 0.0014) compared to normal weight (-9 ± 1 mmHg). The difference in SBP and DBP between ARB users and NoBPMed was significantly greater in those with obesity (SBP: -16 ± 1 mmHg, *P* = 0.0285; DBP: -5 ± 1 mmHg, *P* = 0.0269) compared to normal weight (SBP: -11 ± 1 mmHg, DBP: -1 ± 1 mmHg) and overweight women (DBP: +1 ± 1 mmHg). Conversely, there were no effects of ACE inhibitor or ARB use by BMI on BP in men (*P* > 0.05).

After restricting analysis to individuals on only one type of antihypertensive medication, we observed an interaction effect between ACE inhibitor use and BMI on BP in women (SBP: *P* = 0.0059; DBP: *P* = 0.0014) **(Table 2)**. The difference in SBP and DBP between ACE inhibitor users and NoBPMed was significantly greater in those with obesity (SBP: -15 ± 1 mmHg, *P* = 0.0021; DBP: -7 ± 1 mmHg, *P* = 0.0022) compared to normal weight (SBP: -17 ± 1 mmHg, DBP: -2 ± 1 mmHg). However, in comparison to our main analysis which showed no interaction effect between CCB use and BMI, the restricted analysis found that the difference in SBP between CCB users and non-users was significantly smaller in those with obesity (-6 ± 1 mmHg) compared to overweight (-11 ± 1 mmHg, *P* = 0.0089) and normal weight individuals (-11 ± 1 mmHg, *P* = 0.0298). No other differences were observed.

Association between antihypertensive use and other metabolic risk factors

The association between antihypertensive medication use and FPG, TG, HDL, and WC levels are shown in **Figure 3**. Overall, there was no consistent trend observed between the use of all antihypertensive medications and CVD risk factors. FPG levels were significantly higher in those using ACE inhibitors compared to diuretics (*P* = 0.0125), even when analysis was

restricted to individuals with diabetes ($P = 0.0072$). Triglyceride levels were lower in ARB users and the Other antihypertensive medications compared to those using β-blockers (ARB: $P = 0.0275$; Other: $P = 0.0168$), although very minimal. Neither HDL levels in men and women, nor WC in men differed by antihypertensive medication type ($P > 0.10$). In women, waist circumference was significantly higher with ACE inhibitor use compared to diuretics, CCBs, and NoBPMed (diuretics: $P = 0.0040$; CCB: $P = 0.0343$; NoBPMed: $P = 0.0019$).

Discussion

Although it is clear that all BP medications are associated with reductions in BP, to our knowledge, this is the first study that demonstrated ACE inhibitors and ARBs were associated with bigger differences in BP in women with obesity compared to lean women, while there were minimal differences in men and for other medication types. Nevertheless, we observed higher glucose, and waist circumference levels in women with ACE inhibitor use. Thus, there may be certain antihypertensive medications that are better suited for women with obesity as compared to men, which may be expected given the various mechanisms of action for antihypertensive medication and the known physiological differences by sex and obesity.

The etiology of hypertension differs widely amongst individuals with obesity as a variety of mechanisms directly involved in blood pressure regulation including the sympathetic nervous system (SNS), the renin-angiotensin aldosterone system (RAAS), and fluid balance are altered (41,43). Thus, there may be differences in the expected effectiveness of antihypertensive medications in those with obesity as compared to other BMI categories (108,109). We observed that women with obesity had bigger differences in BP when using ACE inhibitors and ARBs than normal weight and overweight women which may be expected given the known physiology of ACE inhibitors and obesity (130–132). Estrogen has cardio-protective effects in part through decreasing blood pressure by downregulating ACE leading to decreased angiotensin II production (133–135). Conversely, obesity leads to an overexpression of angiotensinogen and increased blood pressure (46,47). Thus, ACE inhibitors and ARBs may have a greater potential to improve hypertension for women than men, particularly in those with obesity (9,136,137). Furthermore, these results are consistent with the "obesity paradox" which suggests that obesity is associated with decreased morbidity and mortality (123,138,139). Given that hypertension is

one of the most important risk factors for premature CVD (113), the superior antihypertensive effect of medications in obesity may play a protective role in risk reduction. Indeed, the INVEST trial found that among patients using ACE inhibitors in combination with CCBs with a history of coronary heart disease and class I obesity had a 49% decreased risk of CV-related mortality, compared to normal-weight patients (123). Therefore, ACE inhibitor use may contribute to the obesity paradox, wherein CVD morbidity and mortality is lowered in those with obesity as a result of superior blood pressure reduction.

We also observed that those taking diuretics with obesity had bigger differences in blood pressure profiles compared to overweight, although minimal. However, there may be a physiological basis for why diuretics may be preferred in obesity (124,140–142). Obesity is associated with increased sodium retention and is often the hallmark of hypertension in obesity (142,143). This is due to the lower rate of natriuresis (urinary sodium excretion) because of reduced natriuretic peptides (144–146). Since diuretics lower blood pressure by promoting natriuresis, they are a logical treatment for hypertension in those with obesity (124). The diuretic class also includes aldosterone antagonists and in addition to a lower rate of natriuresis, aldosterone levels are increased in obesity (51,147,148). Furthermore, a sub-analysis of the ACCOMPLISH trial found that patients with obesity taking a combination of ACE inhibitors and diuretics, were 39%, 60%, and 40% less likely to experience primary CVD endpoints, CVD deaths, and total stroke, respectively, when compared to normal weight individuals taking the same medications. Together this may explain in part why thiazide diuretics may offer more cardiovascular protection in patients with obesity than those who are of lower BMI and that they should be preferred for first-line therapy (124). Therefore, despite our findings, diuretics may still be a reasonable antihypertensive medication choice particularly for those with obesity.

Hypertension in individuals with obesity is commonly associated with increased sympathetic activity, resulting in increased cardiac output (CO) (103). CO is often regulated through activation of β-adrenergic receptors expressed in the heart. Thus, these effects can be antagonized by β-blockade. Some studies have shown BP is more sensitive to adrenergic blockade in obesity than lean individuals (149,150). However, the exact mechanisms by which β-blockade may be more effective in obesity are not known (150). In addition, there are mixed findings wherein we and others observe that there are similar differences in BP with β-blocker use across BMI (118,119). Thus, more research is needed to determine whether there are obesity related differences in BP attained using β-blockers.

We observed that CCBs in combination with other medications were not associated with BP differences by obesity status. This finding is in line with the ACCOMPLISH sub-analysis that suggests that cardiovascular protection, in addition to blood pressure lowering does not differ by BMI in CCB users who were concurrently using ACE inhibitors (124). However, when we restricted the sample to those who were using CCBs alone, we observed smaller BP differences with CCB use in those with obesity as compared to lean which is in accordance with studies that have shown CCB use to be more effective in lean individuals than obesity due to the major hemodynamic action in reducing vascular resistance (149). In conjunction with the superior BP lowering effects in obesity with ACEIs that we observed, the discordant BP medication effects in those with obesity may have been masked in the ACCOMPLISH trial. However, more work in this area is needed to clarify differences in CCB effectiveness by obesity status.

Our study reported higher glucose, and waist circumference levels (in women only) with ACE inhibitor use compared to diuretics. This is in contrast with studies that suggest ACE

inhibitors have beneficial effects on glucose metabolism, lipid profiles and insulin sensitivity, making them particularly attractive for first-line therapy (151,152). ACE inhibitors have been shown to improve glucose metabolism via translocation of the glucose transporters to the cell surface which increases glucose uptake (153–155). However, our results demonstrate elevated glucose levels with ACE inhibitor use compared to diuretics. This difference may be explained in part by the higher ACE inhibitor use, but lower use of diuretics in individuals with diabetes as these differences remained even when the analysis was restricted to individuals with diabetes. Alternatively, there could be an unknown interaction between the different medications. In addition to higher glucose, we also observed higher waist circumference levels in women with ACE inhibitor use compared to diuretics. Diuretics promote diuresis which can lead to weight loss with increases in dose (156). Furthermore, a study by Patil et al. (157) also found that individuals that were administered ACE inhibitors, had an increased waist-hip ratio after 6 months, but did not provide a mechanism behind this observation nor did they examine metabolic differences (157). Therefore, ACE inhibitor use may be associated with differential changes in metabolic risk factors, independent of BMI, but more work is needed to clarify the effects of ACE inhibitors alone and in combination with other medications.

This study had strengths and limitations. The use of NHANES data allows for a large analytic sample that is nationally representative of the US population (129). Additionally, prescription medication, examination, and blood pressure data were collected through personal interviews and questionnaires which have been shown to reduce nonresponse when both data collection modes are used (158). Another strength was the adjustment of many confounding variables associated with blood pressure and medication use. A key limitation in this study includes using cross-sectional survey data which cannot determine causality. Although the blood

pressure medications included in the sample are first-line antihypertensive medications, they are also prescribed to treat other conditions (159) and the specific reason for prescription could not be determined nor could adherence. Furthermore, we were not able to account for dose-related effects; however, we did adjust for the number of antihypertensive medications taken. Overall, this study was weighted to be nationally representative of the US population which demonstrated that certain antihypertensive medications may have clinical impacts on blood pressure and other metabolic risk factors in those with and without obesity.

In conclusion, our study suggested that ACE inhibitors and ARBs may be associated with a greater BP reduction in women with obesity compared to normal weight women, with no differences in BP between antihypertensive medication use by obesity in men. However, we did observe elevated glucose, and WC levels (in women) with ACE inhibitor use. Therefore, obesity status, in addition to potential side effects of antihypertensive medications on cardiometabolic risk should be considered. Future studies should therefore examine the long-term effectiveness of antihypertensive medications on blood pressure, other cardiometabolic risk factors, and morbidity and mortality risk to determine the most appropriate choice of treatment for those with and without obesity.

4.0 GENERAL DISCUSSION

Obesity is a growing global health concern (160). This growing obesity epidemic is a major source of morbidity and mortality because of its association with hypertension, type 2 diabetes, dyslipidemia, certain cancers and major cardiovascular diseases (160). In particular, the effects of obesity on hypertension have long been recognized (9). It is estimated that at least 60% of incident hypertension is directly associated with obesity, and the combination of obesity and hypertension is recognized as a leading cause of CVD risk (9,39,40).

Obesity and related chronic conditions have been associated with increased costs of medical services and have also been linked to higher prescription drug utilization (161). In addition, research has shown that geographical areas with more primary care physicians are 20% less likely to be living with obesity than those living in areas with a shortage of physicians (162). Further, the lack of universal health care in the United States may prevent individuals with obesity to seek medical treatment as they perceive multiple barriers to treatments (163). When coupled with hypertension that manifests with little to no warning signs, diagnosis becomes difficult if blood pressure is not monitored regularly (164). Thus, access to health care for this population improves the diagnosis, treatment, and management of hypertension and many other chronic conditions.

While lifestyle interventions are usually recommended as the initial treatment strategy in lowering blood pressure, optimal blood pressure goals are often not achieved, and pharmacological treatment is needed (9). Antihypertensive therapy has been demonstrated to significantly reduce the risk of death from stroke and CVD by approximately 11%, providing benefits beyond blood pressure lowering (73). Approximately 65% of hypertensive patients use

pharmacological blood pressure treatments (72). Although there are guidelines for the treatment of hypertension for individuals with cardiovascular diseases and type 2 diabetes (75), these guidelines fail to provide recommendations on the management of hypertension using medications in those with obesity (165).

Studies have shown that obesity alters a variety of mechanisms that are involved in blood pressure regulation including SNS, RAAS, and diuresis-natriuresis (43). This thesis demonstrates that antihypertensive medications that act on RAAS may be more advantageous for individuals with obesity, particularly in women. Thus, these findings may add to studies akin to Cataldi et al., that suggest there is no certain antihypertensive medication used as a first choice in the treatment of hypertension for individuals with obesity (166). Moreover, these findings may assist policy makers in establishing guidelines on the management of hypertension for individuals with obesity.

Differences in the treatment and control of blood pressure between men and women have been noted by many studies (167,168). Premenopausal women have been shown to have a lower risk of hypertension compared to men, but this advantage seems to disappear after menopause (167). After 65 years of age, women are more likely to have hypertension than men, and in women between the ages of 65 and 74, the prevalence of hypertension is as high as 58%. In addition, renin activity increases after menopause in women, suggesting antihypertensive therapy targeting RAAS to be more beneficial in BP reduction (169). However, BP control rates in women treated for hypertension still remain lower than men (170). Despite our findings that suggest ACE inhibitors and ARBs may have the greater potential to improve hypertension in women than men, women still exhibit a steeper increase in the risk of a cardiovascular event with increases in BP than men (171). Further, more women than men suffer recurrent strokes within 5

years after their first stroke, with prevalence rates up to 11% higher in women (172). A higher prevalence of stroke may also exist among middle-aged women compared with men, which may be attributed to the growing rates of obesity and metabolic syndrome in middle-aged women (172). Thus, there is a greater need for hypertension awareness, treatment, and management in women than men.

In conclusion, this thesis demonstrates that ACE inhibitors and ARBs may be associated with a greater BP reduction in women with obesity compared to normal weight women, suggesting certain antihypertensive medications may be better suited in individuals with obesity. However, we did observe higher glucose, and WC levels (in women) with ACE inhibitor use as compared to diuretics. Clinically, this may suggest that ACE inhibitors or ARBs may be considered to treat hypertension in obesity. However, when prescribing antihypertensive medications, further consideration should be given to the metabolic risk profile of individual patients.

Table 1. Descriptive characteristics of US adults with hypertension by antihypertensive medication type (NHANES 1999-2014).

	No BP Drug	ACE Inhibitors	β-blockers	Diuretics	CCB	ARB	Other
Participant Characteristics	**(n=5443)**	**(n=4609)**	**(n=4243)**	**(n=5054)**	**(n=3387)**	**(n=2279)**	**(n=974)**
Age, years	49.0 (0.3)	61.0 (0.3)*	63.3 (0.3)*	62.4 (0.3)*	63.6 (0.3)*	62.5 (0.4)*	66.8 (0.5)*
Sex (Female)	45.3 (0.8)	48.0 (0.9)*	53.5 (1.0)*	62.8 (0.8)*	53.4 (1.1)*	57.4 (1.3)*	28.4 (1.9)*
Ethnicity (White)	69.0 (1.5)	74.6 (1.3)*	79.3 (1.1)*	74.9 (1.3)*	68.9 (1.6)	74.4 (1.6)	73.5 (1.9)*
Education (HS or more)	79.7 (0.8)	77.3 (1.0)*	78.0 (1.0)	76.1 (0.9)	74.8 (1.0)*	80.7 (1.0)*	71.6 (2.2)*
Health Insurance (Insured)	78.8 (0.8)	92.6 (0.5)*	93.8 (0.4)*	93.6 (0.6)*	94.2 (0.5)*	95.0 (0.6)*	94.7 (0.9)*
Smoking Status (Smoker)	25.3 (0.9)	16.0 (0.7)*	15.2 (0.8)*	12.8 (0.7)*	14.4 (0.9)*	10.4 (0.9)*	12.6 (1.5)*
Physical Activity Status (Active)	55.2 (1.0)	46.2 (1.1)*	45.9 (1.1)*	43.9 (1.3)*	45.0 (1.0)*	47.5 (1.7)*	45.3 (2.2)*
Body Mass Index (BMI)							
Normal Weight	24.3 (0.7)	16.0 (0.6)*	18.5 (0.7)*	14.5 (0.6)*	18.5 (0.8)*	14.1 (0.9)*	15.8 (1.4)*
Overweight	35.4 (0.8)	33.6 (0.9)	34.9 (0.9)	30.6 (0.9)*	32.6 (0.9)*	31.7 (1.4)*	33.5 (1.7)
Obesity	40.3 (0.9)	50.4 (0.9)*	46.6 (0.9)*	54.9 (1.0)*	48.9 (1.0)*	54.2 (1.4)*	50.7 (1.8)*
Blood Pressure (mmHg)							
Systolic	138 (1)	130 (1)*	132 (1)*	131 (1)*	135 (1)*	133 (1)*	133 (1)*
Diastolic	79 (1)	70 (1)*	70 (1)*	70 (1)*	69 (1)*	70 (1)*	68 (1)*
% control	39.8 (1.1)	70.6 (0.9)*	66.7 (0.9)*	68.7 (0.8)*	62.5 (1.1)*	65.9 (1.2)*	66.0 (1.8)*
Number of BP Meds	--------	2.0 (0.1)	2.3 (0.1)	2.4 (0.1)	2.4 (0.1)	2.3 (0.1)	2.8 (0.1)

Continuous data presented as means (SE), categorical data presented as prevalence, % (SE), estimates weighted to represent the US population. Antihypertensive drug groups are not mutually exclusive. * = Significantly different from no antihypertensive drug group ($P < 0.05$).
ACE=angiotensin-converting enzyme; CCB=calcium channel blocker; ARB=angiotensin receptor blocker; BP=blood pressure; HS=high school; BMI=body mass index; Normal weight=18.5 kg/m^2<BMI<25 kg/m^2; Overweight=25 kg/m^2≤BMI<30 kg/m^2; Obesity=BMI≥30 kg/m^2; SE=standard error.

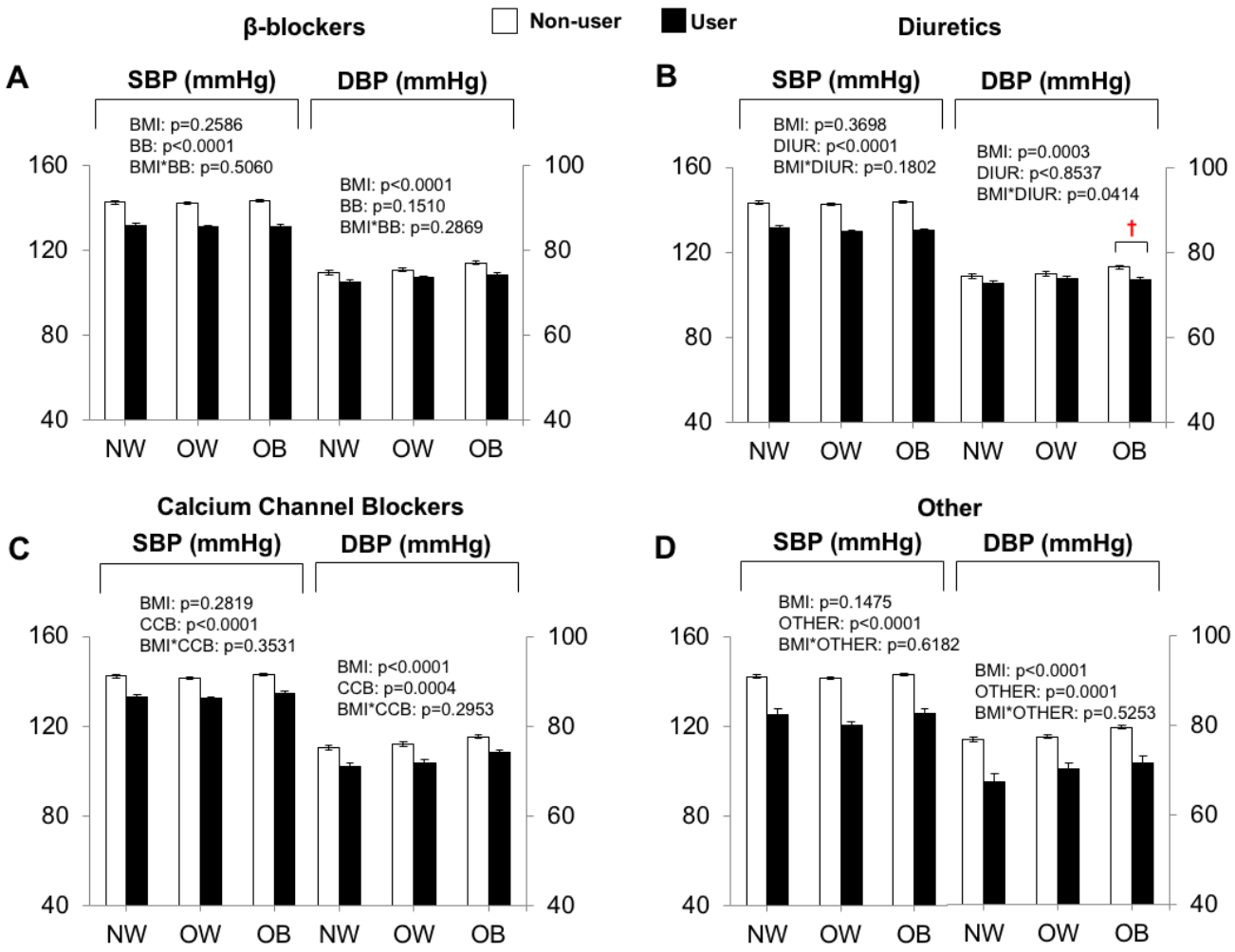


Figure 1. Mean systolic and diastolic blood pressures (mmHg) among hypertensive adults using A) β-blockers, B) Diuretics, C) CCBs and D) Other antihypertensive drugs by BMI category. Sample includes individuals on combination antihypertensive therapy. Means are adjusted for age, sex, ethnicity, health insurance status, smoking status, physical activity, education, and number of antihypertensive medications taken. BMI=body mass index; BB=beta blocker; DIUR=diuretic; CCB=calcium channel blocker; NW=normal weight; OW=overweight; OB=obesity; SBP=systolic blood pressure; DBP=diastolic blood pressure.
† = difference between users and non-users significantly different from overweight ($p<0.05$).

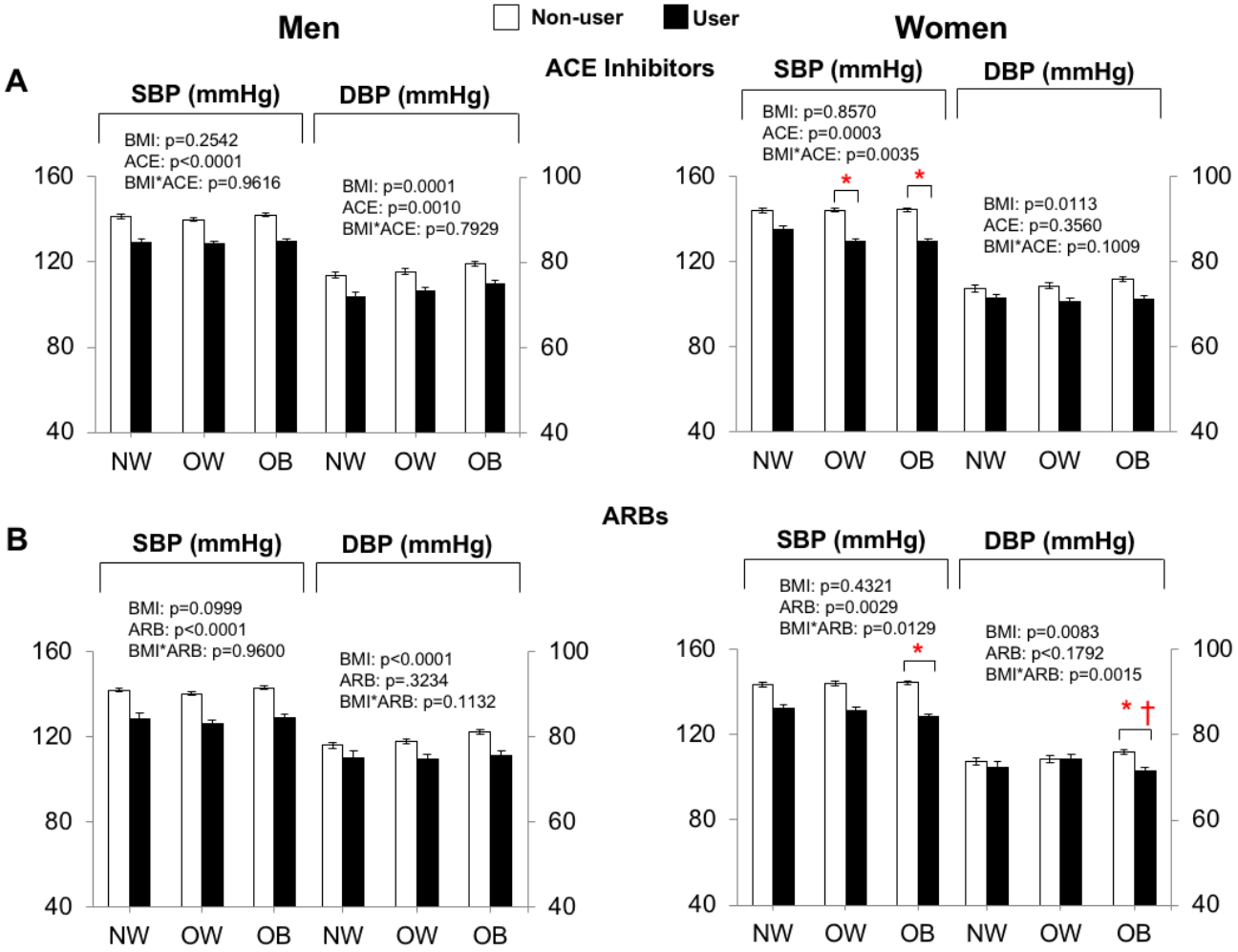


Figure 2. Mean blood pressures (mmHg) among hypertensive adults using A) ACE Inhibitors and B) ARBs by BMI category and sex. Sample includes individuals on combination antihypertensive therapy. Means are adjusted for age, ethnicity, health insurance status, smoking status, physical activity, education, and number of antihypertensive medications taken. BMI=body mass index; ACE=ACE Inhibitor; ARB=angiotensin receptor blocker; NW=normal weight; OW=overweight; OB=obesity; BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure.
* = difference between users and non-users significantly different from normal weight ($p<0.05$),
† = difference between users and non-users significantly different from overweight ($p<0.05$).

Table 2. Blood pressure differences between users and non-users of individuals on antihypertensive monotherapy by BMI category.

	Normal Weight		Overweight		Obesity	
	N (%)	**BP Diff (mmHg)**	***N (%)***	**BP Diff (mmHg)**	***N (%)***	**BP Diff (mmHg)**
SBP (mmHg)						
ACE Inhibitors	305 (17.8)	**M:** -16 (1) **W:** -7 (1)	548 (35.4)	**M:** -11 (1) **W:** -14 (1)*	648 (46.8)	**M:** -12 (1) **W:** -15 (1)*
β-blockers	252 (24.1)	-16 (1)	408 (38.6)	-10 (1)	383 (37.3)	-11 (1)
Diuretics	178 (19.3)	-16 (1)	267 (31.6)	-14 (1)	408 (49.1)	-14 (1)
CCB	189 (24.1)	-11 (1)	284 (34.2)	-11 (1)	291 (41.7)	-6 (1)*†
ARB	103 (17.9)	**M:** -15 (1) **W:** -12 (1)	179 (34.1)	**M:** -14 (1) **W:** -14 (1)	245 (48.0)	**M:** -12 (1) **W:** -15 (1)
Other	47 (27.8)	-20 (1)	73 (36.4)	-20 (1)	57 (35.8)	-17 (1)
DBP (mmHg)						
ACE Inhibitors	305 (17.8)	**M:** -8 (1) **W:** -2 (1)	548 (35.4)	**M:** -7 (1) **W:** -4 (1)	648 (46.8)	**M:** -6 (1) **W:** -7 (1)*†
β-blockers	252 (24.1)	-7 (1)	408 (38.6)	-4 (1)	383 (37.3)	-5 (1)
Diuretics	178 (19.3)	-4 (1)	267 (31.6)	-5 (1)	408 (49.1)	-6 (1)
CCB	189 (24.1)	-7 (1)	284 (34.2)	-7 (1)	291 (41.7)	-4 (1)
ARB	103 (17.9)	**M:** -4 (1) **W:** -4 (1)	179 (34.1)	**M:** -7 (1) **W:** -3 (1)	245 (48.0)	**M:** -8 (1) **W:** -7 (1)
Other	47 (27.8)	-10 (1)	73 (36.4)	-10 (1)	57 (35.8)	-8 (1)

Data presented as mean difference (SE), estimates weighted to represent the US population. Means are adjusted for age, sex, ethnicity, health insurance status, smoking status, physical activity, and education.
ACE=angiotensin-converting enzyme; CCB=calcium channel blocker; ARB=angiotensin receptor blocker; SBP=blood pressure; DBP=diastolic blood pressure; BMI=body mass index; Normal weight=18.5 kg/m^2<BMI<25 kg/m^2; Overweight=25 kg/m^2≤BMI<30 kg/m^2; Obesity=BMI≥30 kg/m^2; SE=standard error; M=Men; W=Women.
* = significantly different from normal weight ($p<0.05$), † = significantly different from overweight ($p<0.05$).

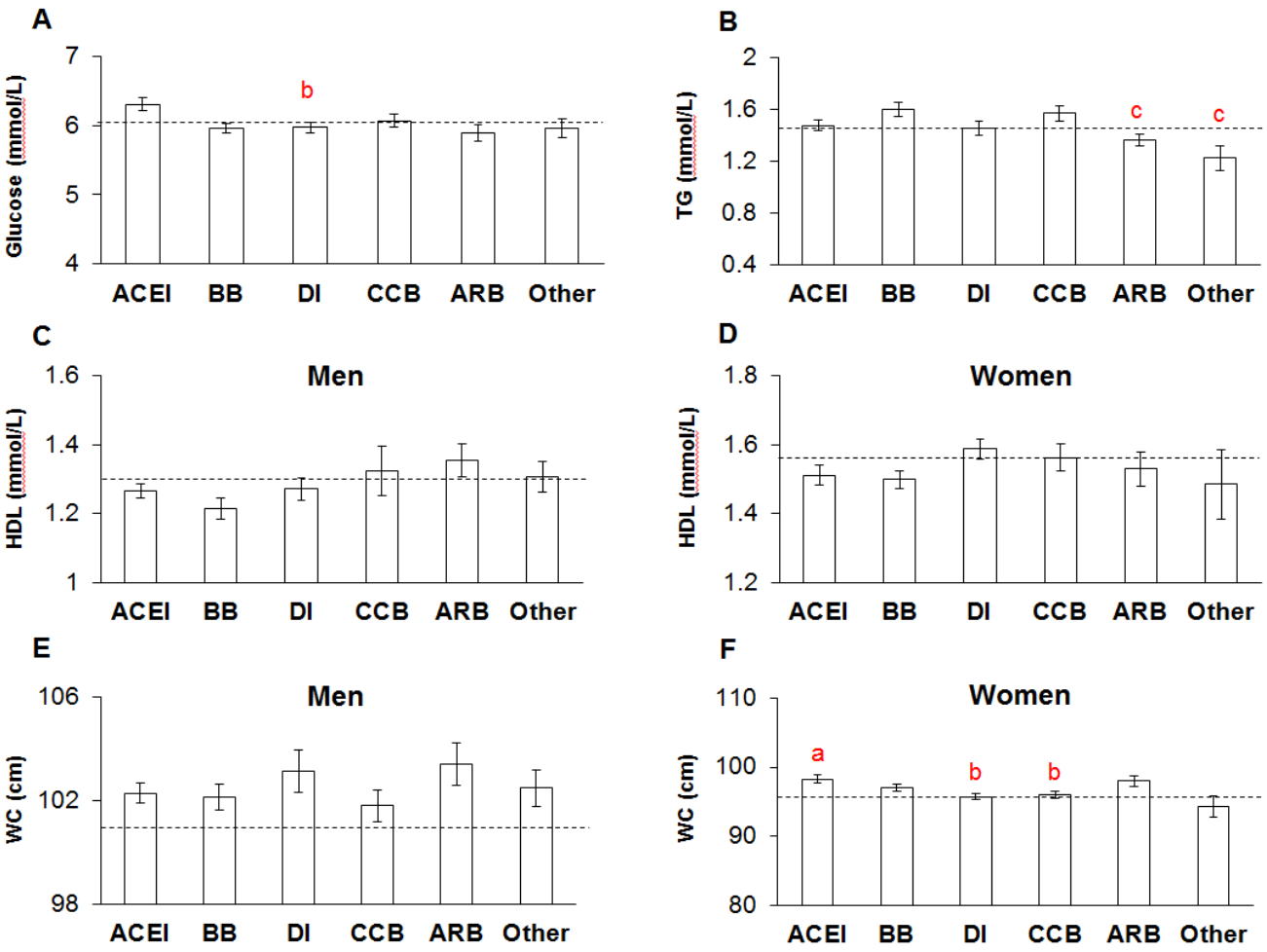


Figure 3. Least squared adjusted means for A) Plasma glucose levels, B) TG levels, C) HDL levels (Men), D) HDL Levels (Women), E) WC (Men), and F) WC (Women) by antihypertensive drug type. All models adjusted for age, sex, BMI, education, health insurance, smoking, and physical activity levels.
ACEI = ACE inhibitors; BB = β-blockers; DI=diuretics; CCB = calcium channel blockers; ARB= angiotensin receptor blockers; TG=triglycerides; HDL= high-density lipoprotein; WC=waist circumference.
a = significantly different from No BP Drug; b = significantly different from ACEI; c = significantly different from BB.
Dashed line is the mean value for No BP Drug

5.0 REFERENCES

1. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation [Internet]. 2006 Feb 14 [cited 2018 Apr 22];113(6):898–918. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16380542
2. Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. Ann Nutr Metab [Internet]. 2015 [cited 2018 Apr 22];66 Suppl 2(Suppl. 2):7–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26045323
3. Obesity and overweight [Internet]. 2017 [cited 2018 Apr 25]. Available from: http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
4. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res [Internet]. 2015 Mar 13 [cited 2017 Sep 22];116(6):991–1006. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25767285
5. WHO | Top 10 causes of death. WHO [Internet]. 2017 [cited 2018 Apr 25]; Available from: http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/
6. Jiang S-Z, Lu W, Zong X-F, Ruan H-Y, Liu Y. Obesity and hypertension. Exp Ther Med [Internet]. 2016 Oct [cited 2018 Apr 25];12(4):2395–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27703502
7. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in Antihypertensive Medication Use and Blood Pressure Control Among United States Adults With HypertensionClinical Perspective. Circulation [Internet]. 2012 [cited 2017 Sep 4];126(17). Available from: http://circ.ahajournals.org/content/126/17/2105
8. Bhan V, Yan RT, Leiter LA, Fitchett DH, Langer A, Lonn E, et al. Relation Between Obesity and the Attainment of Optimal Blood Pressure and Lipid Targets in High Vascular Risk Outpatients; Guidelines Oriented Approach in Lipid Lowering (GOALL) Registry and Vascular Protection (VP) Registry Investigators. AJC [Internet]. 2010 [cited 2018 Apr 25];106:1270–6. Available from: https://www.ajconline.org/article/S0002-9149(10)01375-5/pdf
9. Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, et al. Obesity-Related Hypertension: Pathogenesis, Cardiovascular Risk, and Treatment. J Clin Hypertens [Internet]. 2013 Jan 1 [cited 2017 Sep 22];15(1):14–33. Available from: http://doi.wiley.com/10.1111/jch.12049
10. Carnagarin R, Matthews V, Gregory C, Schlaich MP. Pharmacotherapeutic strategies for treating hypertension in patients with obesity. Expert Opin Pharmacother [Internet]. 2018 Mar 30 [cited 2018 Apr 25];1–9. Available from: https://www.tandfonline.com/doi/full/10.1080/14656566.2018.1458092
11. Obesity Information [Internet]. American Heart Association. 2016 [cited 2017 Sep 25]. Available from: http://www.heart.org/HEARTORG/HealthyLiving/WeightManagement/Obesity/Obesity-Information_UCM_307908_Article.jsp#.WckaTVtSyHs
12. The Facts About High Blood Pressure [Internet]. American Heart Association. 2017 [cited 2017 Sep 25]. Available from:

https://www.heart.org/HEARTORG/Conditions/HighBloodPressure/GettheFactsAboutHighBloodPressure/The-Facts-About-High-Blood-Pressure_UCM_002050_Article.jsp
13. WHO | Hypertension [Internet]. WHO. World Health Organization; 2013 [cited 2017 Sep 25]. Available from: http://www.who.int/topics/hypertension/en/
14. Makridakis S, DiNicolantonio JJ. Hypertension: empirical evidence and implications in 2014. Open Hear [Internet]. 2014 Jul 10 [cited 2017 Sep 22];1(1):e000048. Available from: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2014-000048
15. Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. Indian J Endocrinol Metab [Internet]. 2011 Oct [cited 2017 Aug 9];15 Suppl 4(Suppl4):S281-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22145130
16. Joyner MJ, Limberg JK. Blood pressure regulation: every adaptation is an integration? Eur J Appl Physiol [Internet]. 2014 Mar [cited 2017 Aug 9];114(3):445–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23558925
17. Ackermann U. Regulation of arterial blood pressure. Surg [Internet]. 2004 May 1 [cited 2017 Sep 25];22(5):120a–120f. Available from: http://www.sciencedirect.com/science/article/pii/S0263931906700102
18. Porth CM. Disorders of Blood Pressure Regulation [Internet]. 1st ed. Hannon RA, editor. Phildelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010 [cited 2017 Sep 25]. 1-27 p. Available from: http://downloads.lww.com/wolterskluwer_vitalstream_com/sample-content/9780781766166_Porth/samples/10952-23_CH23.pdf
19. Abboud FMT. The Sympathetic System in Hypertension State-of-the-Art Review. [cited 2017 Jun 26]; Available from: http://hyper.ahajournals.org/content/hypertensionaha/4/3_Pt_2/208.full.pdf
20. Lohmeier TE, Iliescu R. The Sympathetic Nervous System in Obesity Hypertension. Curr Hypertens Rep [Internet]. 2013 Aug 16 [cited 2017 Jul 19];15(4):409–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23677623
21. Swenne CA. Baroreflex sensitivity: mechanisms and measurement. Neth Heart J [Internet]. 2013 Feb [cited 2017 Sep 22];21(2):58–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23179611
22. Skrapari I, Tentolouris N, Perrea D, Bakoyiannis C, Papazafiropoulou A, Katsilambros N. Baroreflex Sensitivity in Obesity: Relationship With Cardiac Autonomic Nervous System Activity*. Obesity [Internet]. 2007 Jul 1 [cited 2017 Jun 28];15(7):1685–93. Available from: http://doi.wiley.com/10.1038/oby.2007.201
23. Sniecinski RM, Wright S, Levy JH. Cardiovascular Pharmacology. In: Cardiothoracic Critical Care [Internet]. Elsevier; 2007 [cited 2017 Oct 10]. p. 33–52. Available from: http://www.crossref.org/deleted_DOI.html
24. Helfand M, Peterson K, Christensen V, Dana T, Thakurta S. Drug Class Review: Beta Adrenergic Blockers: Final Report Update 4. 2009 [cited 2017 Oct 10]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK47168/
25. Gordon RD, Küchel O, Liddle GW, Island DP. Role of the Sympathetic Nervous System in Regulating Renin and Aldosterone Production in Man *. J Clin Invest [Internet]. 1967 Apr 1 [cited 2017 Sep 22];46(4):599–605. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6021207
26. Joyner MJ, Charkoudian N, Wallin BG. Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications. Hypertens (Dallas,

Tex 1979) [Internet]. 2010 Jul [cited 2017 Jul 30];56(1):10–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20497993
27. Hall JE, Guyton AC, Mizelle HL. Role of the renin-angiotensin system in control of sodium excretion and arterial pressure. Acta Physiol Scand Suppl [Internet]. 1990 [cited 2017 Oct 4];591:48–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2220409
28. Cowley AW. Long-term control of arterial blood pressure. Physiol Rev [Internet]. 1992 Jan [cited 2017 Sep 22];72(1):231–300. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1731371
29. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. J Am Soc Nephrol [Internet]. 1999 Apr [cited 2017 Aug 23];10 Suppl 12:S258-65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10201880
30. WHO | Obesity and overweight [Internet]. WHO. World Health Organization; 2016 [cited 2017 Sep 25]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/
31. Body Mass Index (BMI) | Healthy Weight | CDC [Internet]. CDC. 2017 [cited 2017 Sep 25]. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/index.html
32. Pasco JA, Nicholson GC, Brennan SL, Kotowicz MA. Prevalence of Obesity and the Relationship between the Body Mass Index and Body Fat: Cross-Sectional, Population-Based Data. Wang G, editor. PLoS One [Internet]. 2012 Jan 13 [cited 2017 Sep 22];7(1):e29580. Available from: http://dx.plos.org/10.1371/journal.pone.0029580
33. KANNEL WB, BRAND N, SKINNER JJ, DAWBER TR, MCNAMARA PM. The Relation of Adiposity to Blood Pressure and Development of Hypertension. Ann Intern Med [Internet]. 1967 Jul 1 [cited 2017 Jun 21];67(1):48. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-67-1-48
34. Pi-Sunyer X. The medical risks of obesity. Postgrad Med [Internet]. 2009 Nov [cited 2017 Jun 21];121(6):21–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19940414
35. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. JAMA [Internet]. 2014 Feb 26 [cited 2017 Oct 5];311(8):806. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.732
36. Kopelman P. Health risks associated with overweight and obesity. Obes Rev [Internet]. 2007 Mar [cited 2017 May 17];8(s1):13–7. Available from: http://doi.wiley.com/10.1111/j.1467-789X.2007.00311.x
37. Visscher TL, Seidell JC. The Public Health Impact of Obesity. Annu Rev Public Health [Internet]. 2001 May 28 [cited 2017 Sep 22];22(1):355–75. Available from: http://www.annualreviews.org/doi/10.1146/annurev.publhealth.22.1.355
38. Nguyen T, Lau DCW. The Obesity Epidemic and Its Impact on Hypertension. CJCA [Internet]. 2012 [cited 2017 Sep 25];28:326–33. Available from: https://ac.els-cdn.com/S0828282X12000025/1-s2.0-S0828282X12000025-main.pdf?_tid=ba9ac44a-a224-11e7-8af0-00000aacb361&acdnat=1506366610_3a6dbcafbcc535fb4374bf2909a3d4c1
39. Garrison RJ, Kannel WB, Stokes Iii J, Castelli WP. Incidence and Precursors of Hypertension in Young Adults: The Framingham Offspring Study'. Prev Med (Baltim) [Internet]. 1987 [cited 2017 Sep 25];16(1):235–25. Available from: https://ac.els-cdn.com/0091743587900879/1-s2.0-0091743587900879-main.pdf?_tid=5637e37a-a21f-11e7-96e9-00000aacb35e&acdnat=1506364295_39ff228d2ba163878a1b190ffc44f636

40. Hall JE. The kidney, hypertension, and obesity. Hypertens (Dallas, Tex 1979) [Internet]. 2003 Mar 1 [cited 2017 Sep 25];41(3 Pt 2):625–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12623970
41. Dickson ME, Sigmund CD. Genetic basis of hypertension: revisiting angiotensinogen. Hypertens (Dallas, Tex 1979) [Internet]. 2006 Jul 1 [cited 2017 Sep 22];48(1):14–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16754793
42. Rocchini AP. Obesity hypertension. Am J Hypertens [Internet]. 2002 Feb 1 [cited 2017 Sep 25];15(2):S50–2. Available from: https://academic.oup.com/ajh/article-lookup/doi/10.1016/S0895-7061(01)02299-3
43. Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. Hypertens Res [Internet]. 2010 May 1 [cited 2017 Aug 9];33(5):386–93. Available from: http://www.nature.com/doifinder/10.1038/hr.2010.9
44. DeMarco VG, Aroor AR, Sowers JR. The pathophysiology of hypertension in patients with obesity. Nat Rev Endocrinol [Internet]. 2014 Apr 15 [cited 2017 Sep 25];10(6):364–76. Available from: http://www.nature.com/doifinder/10.1038/nrendo.2014.44
45. da Silva AA, do Carmo J, Dubinion J, Hall JE. The role of the sympathetic nervous system in obesity-related hypertension. Curr Hypertens Rep [Internet]. 2009 Jun [cited 2017 Sep 25];11(3):206–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19442330
46. Engeli S, Schling P, Gorzelniak K, Boschmann M, Janke J, Ailhaud G, et al. The adipose-tissue renin–angiotensin–aldosterone system: role in the metabolic syndrome? Int J Biochem Cell Biol [Internet]. 2003 Jun [cited 2017 Jul 30];35(6):807–25. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1357272502003114
47. Yvan-Charvet L, Quignard-Boulangé A. Role of adipose tissue renin–angiotensin system in metabolic and inflammatory diseases associated with obesity. Kidney Int [Internet]. 2011 Jan [cited 2017 Jul 30];79(2):162–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20944545
48. Segura J, Ruilope LM. Obesity, essential hypertension and renin–angiotensin system. Public Health Nutr [Internet]. 2007 Oct 28 [cited 2017 Sep 22];10(10A):1151–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17903324
49. Ailhaud G. Adipose tissue as a secretory organ: from adipogenesis to the metabolic syndrome. C R Biol [Internet]. 2006 Aug [cited 2017 Sep 10];329(8):570–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16860275
50. Kang YS. Obesity associated hypertension: new insights into mechanism. Electrolyte Blood Press [Internet]. 2013 Dec [cited 2017 Oct 6];11(2):46–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24627704
51. Goodfriend TL, Kelley DE, Goodpaster BH, Winters SJ. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. Obes Res [Internet]. 1999 Jul [cited 2017 Sep 10];7(4):355–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10440591
52. Kidambi S, Kotchen TA. Treatment of Hypertension in Obese Patients. Am J Cardiovasc Drugs [Internet]. 2013 Jun 12 [cited 2017 Sep 22];13(3):163–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23579967
53. Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, et al. Effects of Comprehensive Lifestyle Modification on Blood Pressure Control. JAMA [Internet]. 2003 Apr 23 [cited 2017 Sep 22];289(16):2083–93. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/12709466
54. Duman S. Rational approaches to the treatment of hypertension: diet. Kidney Int Suppl [Internet]. 2013 Dec [cited 2017 Aug 28];3(4):343–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25019018
55. Steinberg D, Bennett GG, Svetkey L, LJ A. The DASH Diet, 20 Years Later. JAMA [Internet]. 2017 Apr 18 [cited 2017 Aug 26];317(15):1529. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2017.1628
56. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. N Engl J Med [Internet]. 2001 Jan 4 [cited 2017 Sep 22];344(1):3–10. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM200101043440101
57. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure. N Engl J Med [Internet]. 1997 Apr 17 [cited 2017 Jul 19];336(16):1117–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9099655
58. Soltani S, Shirani F, Chitsazi MJ, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Obes Rev [Internet]. 2016 May 1 [cited 2017 Sep 22];17(5):442–54. Available from: http://doi.wiley.com/10.1111/obr.12391
59. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of Weight Reduction on Blood Pressure: A Meta-Analysis of Randomized Controlled Trials. Hypertension [Internet]. 2003 Nov 1 [cited 2017 Sep 22];42(5):878–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12975389
60. Mellen PB, Gao SK, Vitolins MZ, Goff DC. Deteriorating Dietary Habits Among Adults With Hypertension. Arch Intern Med [Internet]. 2008 Feb 11 [cited 2017 Sep 22];168(3):308. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18268173
61. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-Style Diet and Risk of Coronary Heart Disease and Stroke in Women. Arch Intern Med [Internet]. 2008 Apr 14 [cited 2017 Sep 22];168(7):713. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18413553
62. Semlitsch T, Jeitler K, Hemkens LG, Horvath K, Nagele E, Schuermann C, et al. Increasing Physical Activity for the Treatment of Hypertension: A Systematic Review and Meta-Analysis. Sport Med [Internet]. 2013 Oct 28 [cited 2017 Jul 31];43(10):1009–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23812856
63. Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension: an update. Sports Med [Internet]. 2000 Sep [cited 2017 Jul 31];30(3):193–206. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10999423
64. Carroll JF, Kyser CK. Exercise training in obesity lowers blood pressure independent of weight change. Med Sci Sports Exerc [Internet]. 2002 Apr [cited 2017 Sep 22];34(4):596–601. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11932566
65. Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. Eur J Cardiovasc Prev Rehabil [Internet]. 2007 Feb 28 [cited 2017 Jul 31];14(1):12–7. Available from: http://journals.sagepub.com/doi/10.1097/HJR.0b013e3280128bbb

66. Chen C-Y, Bonham AC. Postexercise hypotension: central mechanisms. Exerc Sport Sci Rev [Internet]. 2010 Jul [cited 2017 Aug 28];38(3):122–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20577060
67. Ishikawa-Takata K, Ohta T, Tanaka H. How much exercise is required to reduce blood pressure in essential hypertensives: a dose-response study. Am J Hypertens [Internet]. 2003 Aug [cited 2017 Aug 28];16(8):629–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12878367
68. Blumenthal JA, Sherwood A, Gullette EC, Babyak M, Waugh R, Georgiades A, et al. Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. Arch Intern Med [Internet]. 2000 Jul 10 [cited 2017 Sep 10];160(13):1947–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10888969
69. Bacon SL, Sherwood A, Hinderliter A, Blumenthal JA. Effects of Exercise, Diet and Weight Loss on High Blood Pressure. Sport Med [Internet]. 2004 [cited 2017 Aug 28];34(5):307–16. Available from: http://link.springer.com/10.2165/00007256-200434050-00003
70. Allen K, Morey MC. Physical Activity and Adherence. In: Improving Patient Treatment Adherence [Internet]. New York, NY: Springer New York; 2010 [cited 2017 Sep 22]. p. 9–38. Available from: http://link.springer.com/10.1007/978-1-4419-5866-2_2
71. CDC Online Newsroom | Press Release | One in five adults meet overall physical activity guidelines [Internet]. CDC. 2013 [cited 2017 Sep 25]. Available from: https://www.cdc.gov/media/releases/2013/p0502-physical-activity.html
72. Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. Circulation [Internet]. 2012 Oct 23 [cited 2017 Sep 22];126(17):2105–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23091084
73. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke [Internet]. 2014 Dec [cited 2017 Sep 25];45(12):3754–832. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25355838
74. Chobanian A V., Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<SUBTITLE>The JNC 7 Report</SUBTITLE> JAMA [Internet]. 2003 May 21 [cited 2017 Sep 22];289(19):2560. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12748199
75. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. JAMA [Internet]. 2014 Feb 5 [cited 2017 Jul 9];311(5):507. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2013.284427
76. Brater DC. Diuretic Therapy. Wood AJJ, editor. N Engl J Med [Internet]. 1998 Aug 6 [cited 2017 Sep 22];339(6):387–95. Available from: http://www.nejm.org/doi/10.1056/NEJM199808063390607
77. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in Obesity Among US Adults, 1999-2008. JAMA [Internet]. 2010 Jan 20 [cited 2017 Jun 26];303(3):235.

Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2009.2014
78. Reyes A. Diuretics in the therapy of hypertension. J Hum Hypertens [Internet]. 2002 [cited 2017 Jul 7];16:78–83. Available from: www.nature.com/jhh
79. Anderton JL, Kincaid'Smith P. Diuretics I: Physiological and Pharmacological Considerations. Drugs [Internet]. 1971;1(1):54–81. Available from: https://doi.org/10.2165/00003495-197101010-00004
80. Ives HE. Basic & Clinical Phamacology [Internet]. 12th ed. Katzung, Bertram G., Masters, Susan B. TAJ, editor. San Francisco: The McGraw-Hill Companies, Inc; 2012 [cited 2017 Sep 25]. 251-255 p. Available from: http://file.zums.ac.ir/ebook/188-Basic and Clinical Pharmacology 12th Edition=Bertram Katzung Susan Masters Anthony Trevor=007.pdf
81. Horisberger J-D, Giebisch G. Potassium-Sparing Diuretics. Kidney Blood Press Res [Internet]. 1987 [cited 2017 Sep 22];10(3–4):198–220. Available from: http://www.karger.com/doi/10.1159/000173130
82. Düsing R. Pharmacological interventions into the renin–angiotensin system with ACE inhibitors and angiotensin II receptor antagonists: effects beyond blood pressure lowering. Ther Adv Cardiovasc Dis [Internet]. 2016 Jun 27 [cited 2017 Sep 22];10(3):151–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27122491
83. Laverman GD, Remuzzi G, Ruggenenti P. ACE inhibition versus angiotensin receptor blockade: which is better for renal and cardiovascular protection? J Am Soc Nephrol [Internet]. 2004 Jan 1 [cited 2017 Jul 31];15 Suppl 1(1 suppl):S64-70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14684676
84. Burnier M, Brunner HR. Angiotensin II receptor antagonists. Lancet (London, England) [Internet]. 2000 Feb 19 [cited 2017 Jul 31];355(9204):637–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10696996
85. Kon V, Fogo A, Ichikawa I, Hellings SE, Bills T. Bradykinin causes selective efferent arteriolar dilation during angiotensin I converting enzyme inhibition. Kidney Int [Internet]. 1993 Sep [cited 2017 Jul 31];44(3):545–50. Available from: http://linkinghub.elsevier.com/retrieve/pii/S008525381558160X
86. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. In: Li EC, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2014 [cited 2017 Sep 25]. Available from: http://doi.wiley.com/10.1002/14651858.CD009096.pub2
87. Wallukat G. The β-Adrenergic Receptors. Herz [Internet]. 2002 Nov 1 [cited 2017 Jul 6];27(7):683–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12439640
88. Gorre F, Vandekerckhove H. Beta-blockers: focus on mechanism of action. Which beta-blocker, when and why? Acta Cardiol [Internet]. 2010 Oct [cited 2017 Jul 6];65(5):565–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21125979
89. Frishman WH. Beta-Adrenergic Receptor Blockers in Hypertension: Alive and Well. Prog Cardiovasc Dis [Internet]. 2016 Nov 1 [cited 2017 Oct 10];59(3):247–52. Available from: http://www.sciencedirect.com/science/article/pii/S0033062016301220
90. Van Bortel LM, Ament AJ. Selective versus nonselective beta adrenoceptor antagonists in hypertension. Pharmacoeconomics [Internet]. 1995 Dec [cited 2017 Jul 31];8(6):513–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10160080
91. Wilkinson R. Beta-blockers and renal function. Drugs [Internet]. 1982 Mar [cited 2017 Jul

31];23(3):195–206. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6122552
92. Tocci G, Battistoni A, Passerini J, Musumeci MB, Francia P, Ferrucci A, et al. Calcium Channel Blockers and Hypertension. J Cardiovasc Pharmacol Ther [Internet]. 2015 Mar 14 [cited 2017 Jul 9];20(2):121–30. Available from: http://journals.sagepub.com/doi/10.1177/1074248414555403
93. Millard RW, Lathrop DA, Grupp G, Ashraf M, Grupp IL, Schwartz A. Differential cardiovascular effects of calcium channel blocking agents: Potential mechanisms. Am J Cardiol [Internet]. 1982 [cited 2017 Jul 9];49(3):499–506. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002914982800027
94. Scholz H. Pharmacological aspects of calcium channel blockers. Cardiovasc drugs Ther [Internet]. 1997 Jan [cited 2017 Jul 9];10 Suppl 3:869–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9126675
95. Trenkwalder P. Antihypertensive treatment with calcium channel blockers: pharmacological pornography or useful intervention? Nephrol Dial Transplant [Internet]. 2004 Jan 1 [cited 2017 Aug 2];19(1):17–20. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfg431
96. Leenen FH, Ruzicka M, Huang BS. Central sympathoinhibitory effects of calcium channel blockers. Curr Hypertens Rep [Internet]. 2001 Aug [cited 2017 Aug 2];3(4):314–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11470014
97. Scholze J, Sharma AM. [Treatment of hypertension in obesity]. Herz [Internet]. 2001 May [cited 2017 Aug 2];26(3):209–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11413801
98. Jesky MD, Hayer MK, Thomas M, Dasgupta I. Do Obese Individuals With Hypertension Have More Difficult-to-Control Blood Pressure and End Organ Damage Than Their Nonobese Counterparts? J Clin Hypertens [Internet]. 2015 Jun 1 [cited 2017 Sep 22];17(6):466–72. Available from: http://doi.wiley.com/10.1111/jch.12532
99. Sharma AM. Is there a rationale for angiotensin blockade in the management of obesity hypertension? Hypertens (Dallas, Tex 1979) [Internet]. 2004 Jul [cited 2017 May 17];44(1):12–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15173127
100. Jandeleit-Dahm KAM, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. J Hypertens [Internet]. 2005 Mar [cited 2017 Aug 2];23(3):463–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15716683
101. Allcock DM, Sowers JR. Best Strategies for Hypertension Management in Type 2 Diabetes and Obesity. Curr Diab Rep [Internet]. 2010 Apr 2 [cited 2017 Aug 2];10(2):139–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20425573
102. Dentali F, Sharma AM, Douketis JD. Management of hypertension in overweight and obese patients: a practical guide for clinicians. Curr Hypertens Rep [Internet]. 2005 Oct [cited 2017 Aug 2];7(5):330–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16157073
103. Pischon T, Sharma AM. Use of beta-blockers in obesity hypertension: potential role of weight gain. Obes Rev [Internet]. 2001 Nov [cited 2017 Aug 2];2(4):275–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12119998
104. Neil S., Beck JD, Clark M. Combination Antihypertensive Drugs: Recommendations for Use. Am Fam Physician [Internet]. 1970 May 15 [cited 2017 Sep 25];61(10):3049. Available from: http://www.aafp.org/afp/2000/0515/p3049.html

105. Kjeldsen SE, Julius S, Mancia G, McInnes GT, Hua T, Weber MA, et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertens [Internet]. 2006 Jul [cited 2017 Aug 2];24(7):1405–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16794491
106. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of Obesity on the Pharmacokinetics of Drugs in Humans. Clin Pharmacokinet [Internet]. 2010 Feb [cited 2017 Aug 28];49(2):71–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20067334
107. Leykin Y, Miotto L, Pellis T. Pharmacokinetic considerations in the obese. Best Pract Res Clin Anaesthesiol [Internet]. 2011 Mar [cited 2017 Jul 9];25(1):27–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21516911
108. Morrish GA, Pai MP, Green B. The effects of obesity on drug pharmacokinetics in humans. Expert Opin Drug Metab Toxicol [Internet]. 2011 Jun 22 [cited 2017 Sep 22];7(6):697–706. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21417960
109. Brill MJE, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, Knibbe CAJ. Impact of Obesity on Drug Metabolism and Elimination in Adults and Children. Clin Pharmacokinet [Internet]. 2012 May 1 [cited 2017 Sep 22];51(5):277–304. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22448619
110. Katie S. Buehler PB, Abigail M. Yancey PB. Underdosing in obesity—an epidemic: focus on antibiotics. Formulary [Internet]. 2013 Jul 4 [cited 2017 Sep 22]; Available from: http://formularyjournal.modernmedicine.com/formulary-journal/content/tags/antibiotics/underdosing-obesity-epidemic-focus-antibiotics
111. Russell H, Bourne K. DRUG DOSE ADJUSTMENTS IN OBESE PAEDIATRIC PATIENTS. Arch Dis Child [Internet]. 2015 Jun 18 [cited 2017 Sep 22];100(6):e1.33-e1. Available from: http://adc.bmj.com/lookup/doi/10.1136/archdischild-2015-308634.39
112. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation [Internet]. 2015 Oct 27 [cited 2017 Sep 25];132(17):1667–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26503749
113. Lawes CMM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancet (London, England) [Internet]. 2008 May 3 [cited 2017 Sep 22];371(9623):1513–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673608606558
114. MacMahon S, Cutler J, Brittain E, Higgins M. Obesity and hypertension: epidemiological and clinical issues. Eur Heart J [Internet]. 1987 May [cited 2017 Sep 4];8 Suppl B:57–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3301356
115. Narkiewicz K. Obesity and hypertension--the issue is more complex than we thought. Nephrol Dial Transplant [Internet]. 2006 Feb 1 [cited 2017 Sep 22];21(2):264–7. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfi290
116. Barnes AS. The epidemic of obesity and diabetes: trends and treatments. Texas Hear Inst J [Internet]. 2011 [cited 2017 Sep 22];38(2):142–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21494521
117. Artham SM, Lavie CJ, Milani R V, Ventura HO. Obesity and hypertension, heart failure, and coronary heart disease-risk factor, paradox, and recommendations for weight loss. Ochsner J [Internet]. 2009 [cited 2017 Sep 22];9(3):124–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21603427
118. Wójcicki J, Jaroszynska M, Droździk M, Pawlik A, Gawrónska-Szklarz B, Sterna R.

Comparative pharmacokinetics and pharmacodynamics of propranolol and atenolol in normolipaemic and hyperlipidaemic obese subjects. Biopharm Drug Dispos [Internet]. 2003 [cited 2018 Apr 3];24(5):211–8. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1002/bdd.357
119. Cheymol G, Woestenborghs R, Snoeck E, Ianucci R, Le Moing JP, Naditch L, et al. Pharmacokinetic study and cardiovascular monitoring of nebivolol in normal and obese subjects. Eur J Clin Pharmacol [Internet]. 1997 [cited 2018 Apr 4];51(6):493–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9112066
120. Huizinga MM, Bleich SN, Beach MC, Clark JM, Cooper LA. Disparity in physician perception of patients' adherence to medications by obesity status. Obesity (Silver Spring) [Internet]. 2010 Oct [cited 2018 Apr 4];18(10):1932–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20186132
121. van Onzenoort HAW, Menger FE, Neef C, Verberk WJ, Kroon AA, de Leeuw PW, et al. Participation in a clinical trial enhances adherence and persistence to treatment: a retrospective cohort study. Hypertens (Dallas, Tex 1979) [Internet]. 2011 Oct 1 [cited 2018 Mar 28];58(4):573–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21825228
122. Cohen AT, Goto S, Schreiber K, Torp-Pedersen C. Why do we need observational studies of everyday patients in the real-life setting?: Table 1. Eur Hear J Suppl [Internet]. 2015 Jul 10 [cited 2018 Mar 28];17(suppl D):D2–8. Available from: https://academic.oup.com/eurheartjsupp/article-lookup/doi/10.1093/eurheartj/suv035
123. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-DeHoff RM, Zhou Q, et al. Obesity Paradox in Patients with Hypertension and Coronary Artery Disease. Am J Med [Internet]. 2007 Oct [cited 2018 Feb 19];120(10):863–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17904457
124. Weber MA, Jamerson K, Bakris GL, Weir MR, Zappe D, Zhang Y, et al. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. Lancet [Internet]. 2013 Feb 16 [cited 2018 Jan 11];381(9866):537–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23219284
125. Blood Pressure Lowering Treatment Trialists' Collaboration, Ying A, Arima H, Czernichow S, Woodward M, Huxley R, et al. Effects of blood pressure lowering on cardiovascular risk according to baseline body-mass index: a meta-analysis of randomised trials. Lancet (London, England) [Internet]. 2015 Mar 7 [cited 2018 Mar 13];385(9971):867–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25468168
126. Raicu M, Pojoga L, Simionescu N, Simionescu M. The effect of ACE inhibitors on atheroma formation is potentiated by association with a calcium channel blocker. A biochemical and ultrastructural study. J Submicrosc Cytol Pathol [Internet]. 1997 Jul [cited 2018 Mar 19];29(3):317–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9267040
127. Lüscher TF, Noll G. The pathogenesis of cardiovascular disease: role of the endothelium as a target and mediator. Atherosclerosis [Internet]. 1995 Dec [cited 2017 Aug 28];118 Suppl:S81-90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8821468
128. NHANES - National Health and Nutrition Examination Survey Homepage [Internet]. CDC/National Center for Health Statistics. 2017 [cited 2017 Sep 25]. Available from: https://www.cdc.gov/nchs/nhanes/index.htm

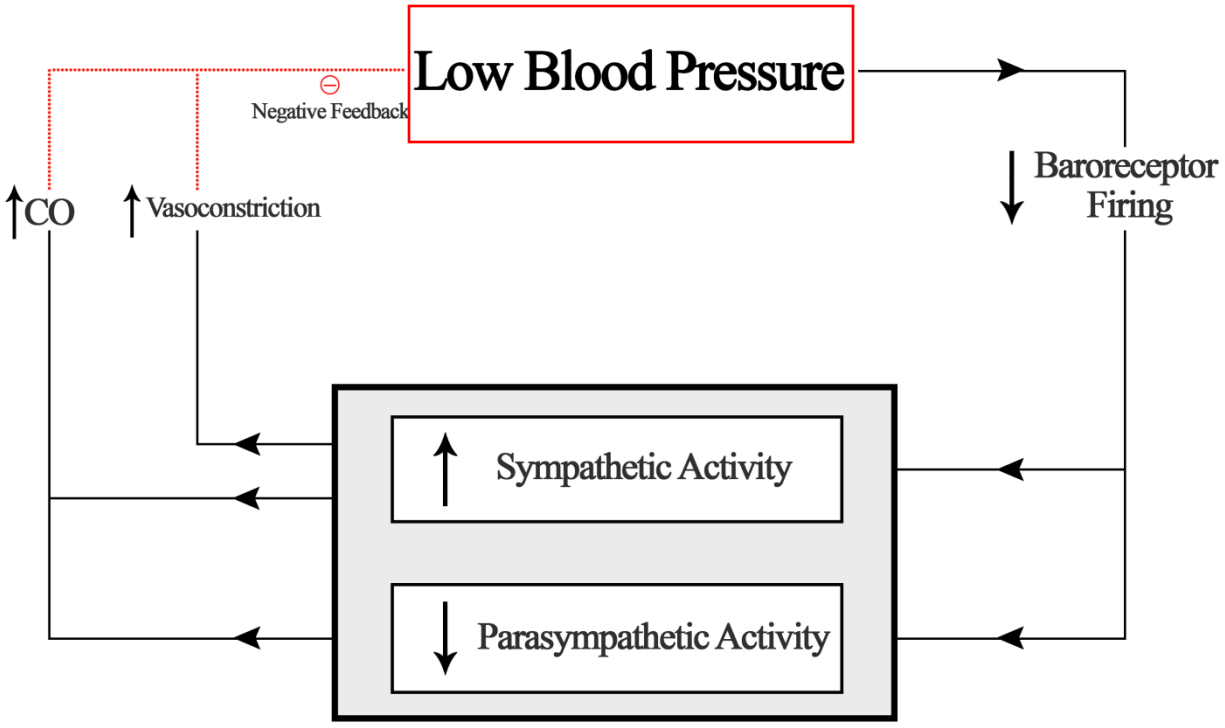
129. NHANES - About the National Health and Nutrition Examination Survey [Internet]. CDC/National Center for Health Statistics. 2017 [cited 2017 Sep 25]. Available from: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm
130. Shimamoto K. ACE Inhibitors and ARBs for Obesity-Related Hypertension. Immunol Endocr Metab Agents Med Chem [Internet]. 2010 Jun 1 [cited 2018 Jan 10];10(2):55–8. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1871-5222&volume=10&issue=2&spage=55
131. Cooper R, McFarlane-Anderson N, Bennett F, Wilks R, Puras A, Tewksbury D, et al. ACE, angiotensinogen and obesity: a potential pathway leading to hypertension. J Hum Hypertens [Internet]. 1997 Feb 18 [cited 2018 Jan 10];11(2):107–11. Available from: http://www.nature.com/articles/1000391
132. Sharma AM, Engeli S. Obesity and the renin– angiotensin–aldosterone system. Expert Rev Endocrinol Metab [Internet]. 2006 Mar 10 [cited 2017 Jul 19];1(2):255–64. Available from: http://www.tandfonline.com/doi/full/10.1586/17446651.1.2.255
133. Ashraf MS, Vongpatanasin W. Estrogen and hypertension. Curr Hypertens Rep [Internet]. 2006 Oct [cited 2017 Nov 1];8(5):368–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16965722
134. Maranon R, Reckelhoff JF. Sex and gender differences in control of blood pressure. Clin Sci (Lond) [Internet]. 2013 Oct [cited 2017 Oct 31];125(7):311–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23746374
135. O'Donnell E, Floras JS, Harvey PJ. Estrogen status and the renin angiotensin aldosterone system. AJP Regul Integr Comp Physiol [Internet]. 2014 Sep 1 [cited 2017 Oct 31];307(5):R498–500. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24944241
136. Eshtiaghi R, Esteghamati A, Nakhjavani M. Menopause is an independent predictor of metabolic syndrome in Iranian women. Maturitas [Internet]. 2010 Mar [cited 2018 Jan 10];65(3):262–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0378512209004034
137. Mallamaci F, Ruggenenti P, Perna A, Leonardis D, Tripepi R, Tripepi G, et al. ACE inhibition is renoprotective among obese patients with proteinuria. J Am Soc Nephrol [Internet]. 2011 Jun [cited 2017 Nov 1];22(6):1122–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21527660
138. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. Diabetes Care [Internet]. 2013 Aug [cited 2017 Dec 18];36 Suppl 2(Suppl 2):S276-81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23882059
139. Esler M, Lambert G, Schlaich M, Dixon J, Sari CI, Lambert E. Obesity Paradox in Hypertension: Is This Because Sympathetic Activation in Obesity-Hypertension Takes a Benign Form? Hypertens (Dallas, Tex 1979) [Internet]. 2018 Jan 1 [cited 2018 Mar 13];71(1):22–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29158358
140. Naumnik B, Myśliwiec M. Renal consequences of obesity. Med Sci Monit [Internet]. 2010 Aug [cited 2018 Mar 13];16(8):RA163-70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20671624
141. Messerli FH, Christie B, DeCarvalho JG, Aristimuno GG, Suarez DH, Dreslinski GR, et al. Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion, and plasma renin activity. Arch Intern Med [Internet]. 1981 Jan [cited 2017 May 17];141(1):81–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7004372

142. Re RN. Obesity-related hypertension. Ochsner J [Internet]. 2009 [cited 2018 Mar 13];9(3):133–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21603428
143. Barrett-Connor E, Khaw KT. Is hypertension more benign when associated with obesity? Circulation [Internet]. 1985 Jul 1 [cited 2018 Jan 14];72(1):53–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4006136
144. Lavie CJ, Mehra MR, Milani R V. Obesity and heart failure prognosis: paradox or reverse epidemiology? Eur Heart J [Internet]. 2005 Jan 1 [cited 2017 Dec 18];26(1):5–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15615792
145. Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol [Internet]. 2004 May 5 [cited 2017 Dec 18];43(9):1590–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15120816
146. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: Mechanisms and diagnostic implications for heart failure. Int J Cardiol [Internet]. 2014 Oct 20 [cited 2018 Mar 13];176(3):611–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25156856
147. Huby A-C, Belin EJ, Chantemèle D. Reviving the use of aldosterone inhibitors in treating hypertension in obesity Huby AC, Belin De Chantemèle EJ. Reviving the use of aldosterone inhibitors in treating hypertension in obesity. Am J Physiol Regul Integr Comp Physiol [Internet]. 2015 [cited 2017 Dec 8];309:1065–7. Available from: http://www.physiology.org/doi/pdf/10.1152/ajpregu.00133.2015
148. Kawarazaki W, Fujita T. The Role of Aldosterone in Obesity-Related Hypertension. Am J Hypertens [Internet]. 2016 Apr [cited 2018 Jan 14];29(4):415–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26927805
149. Schmieder RE, Gatzka C, Schächinger H, Schobel H, Rüddel H. Obesity as a determinant for response to antihypertensive treatment. BMJ [Internet]. 1993 Aug 28 [cited 2018 Mar 29];307(6903):537–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8400973
150. Wofford M, H L, I S, C B, J W, M C, et al. Antihypertensive effect of α- and β-adrenergic blockade in obese and lean hypertensive subjects. Am J Hypertens [Internet]. 2001 Jul 1 [cited 2017 Jul 9];14(7):694–8. Available from: https://academic.oup.com/ajh/article-lookup/doi/10.1016/S0895-7061(01)01293-6
151. Jordan J, Yumuk V, Schlaich M, Nilsson PM, Zahorska-Markiewicz B, Grassi G, et al. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension. J Hypertens [Internet]. 2012 Jun [cited 2017 Oct 31];30(6):1047–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22573071
152. Reisin E, Weir MR, Falkner B, Hutchinson HG, Anzalone DA, Tuck ML. Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebo-controlled trial. Treatment in Obese Patients With Hypertension (TROPHY) Study Group. Hypertens (Dallas, Tex 1979) [Internet]. 1997 Jul [cited 2018 Mar 13];30(1 Pt 1):140–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9231834
153. Luther JM, Brown NJ. The renin-angiotensin-aldosterone system and glucose homeostasis. Trends Pharmacol Sci [Internet]. 2011 Dec [cited 2018 Feb 5];32(12):734–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21880378
154. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Rep [Internet]. 2013 Feb [cited 2018 Feb 5];15(1):59–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23242734

155. Abuissa H, Jones PG, Marso SP, O'Keefe JH. Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers for Prevention of Type 2 Diabetes. J Am Coll Cardiol [Internet]. 2005 Sep 6 [cited 2018 Jan 28];46(5):821–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0735109705012714
156. Freis ED, Reda DJ, Materson BJ. Volume (weight) loss and blood pressure response following thiazide diuretics. Hypertens (Dallas, Tex 1979) [Internet]. 1988 Sep 1 [cited 2018 Apr 26];12(3):244–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3049338
157. Patil MR, Mishra A, Jain N, Gutch M, Tewari R. Weight loss for reduction of proteinuria in diabetic nephropathy: Comparison with angiotensin-converting enzyme inhibitor therapy. Indian J Nephrol [Internet]. 2013 Mar [cited 2018 Jan 28];23(2):108–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23716916
158. De Leeuw ED. To Mix or Not to Mix Data Collection Modes in Surveys. [cited 2017 Oct 30]; Available from: https://search.proquest.com/docview/1266791766?pq-origsite=gscholar
159. Akbar S, Alorainy MS. The current status of beta blockers' use in the management of hypertension. Saudi Med J [Internet]. 2014 Nov [cited 2017 Dec 10];35(11):1307–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25399206
160. Leggio M, Lombardi M, Caldarone E, Severi P, D'Emidio S, Armeni M, et al. The relationship between obesity and hypertension: an updated comprehensive overview on vicious twins. Hypertens Res [Internet]. 2017 Dec 5 [cited 2018 May 14];40(12):947–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28978986
161. Musich S, MacLeod S, Bhattarai GR, Wang SS, Hawkins K, Bottone FG, et al. The Impact of Obesity on Health Care Utilization and Expenditures in a Medicare Supplement Population. Gerontol Geriatr Med [Internet]. 2016 [cited 2018 Jun 11];2:2333721415622004. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28138482
162. Gaglioti AH, Petterson S, Bazemore A, Phillips R. Access to Primary Care in US Counties Is Associated with Lower Obesity Rates. J Am Board Fam Med [Internet]. 2016 Mar 1 [cited 2018 Jun 11];29(2):182–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26957374
163. Ciao AC, Latner JD, Durso LE. Treatment seeking and barriers to weight loss treatments of different intensity levels among obese and overweight individuals. Eat Weight Disord [Internet]. 2012 Mar [cited 2018 Jun 11];17(1):e9-16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22751277
164. High Blood Pressure (Hypertension) Information | cdc.gov [Internet]. 2018 [cited 2018 Jun 11]. Available from: https://www.cdc.gov/bloodpressure/index.htm
165. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. JAMA [Internet]. 2014 Feb 5 [cited 2017 Oct 5];311(5):507. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2013.284427
166. Cataldi M, di Geronimo O, Trio R, Scotti A, Memoli A, Capone D, et al. Utilization of antihypertensive drugs in obesity-related hypertension: a retrospective observational study in a cohort of patients from Southern Italy. BMC Pharmacol Toxicol [Internet]. 2016 Dec 16 [cited 2018 Jun 4];17(1):9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26980335

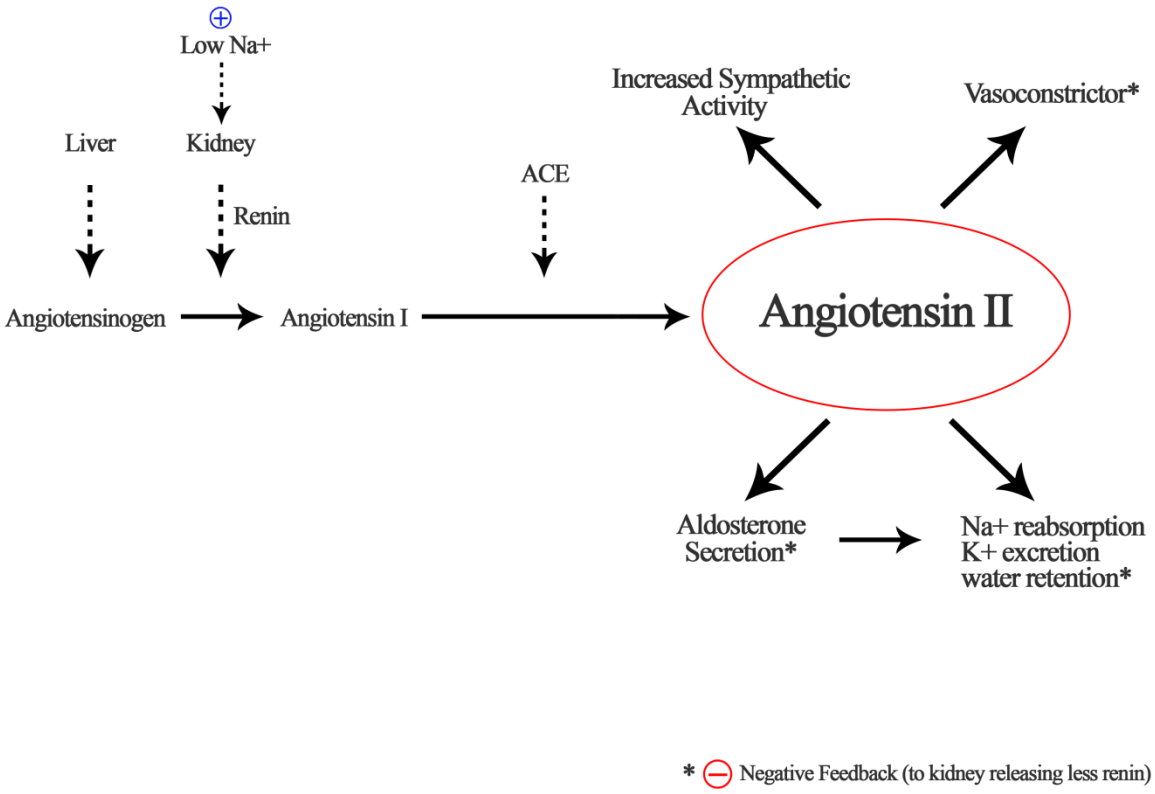
167. Gudmundsdottir H, Høieggen A, Stenehjem A, Waldum B, Os I. Hypertension in women: latest findings and clinical implications. Ther Adv Chronic Dis [Internet]. 2012 May [cited 2018 Jun 11];3(3):137–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23251774
168. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. Eur Heart J [Internet]. 1999 Mar [cited 2018 Jun 11];20(6):447–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10213348
169. Duerrschmidt N, Wippich N, Goettsch W, Broemme H-J, Morawietz H. Endothelin-1 Induces NAD(P)H Oxidase in Human Endothelial Cells. Biochem Biophys Res Commun [Internet]. 2000 Mar 24 [cited 2018 Jun 11];269(3):713–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10720482
170. Igho Pemu P, Ofili E. Hypertension in women: part I. J Clin Hypertens (Greenwich) [Internet]. 2008 May [cited 2018 Jun 12];10(5):406–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18453801
171. Gillis EE, Sullivan JC. Sex Differences in Hypertension: Recent Advances. Hypertens (Dallas, Tex 1979) [Internet]. 2016 Dec 1 [cited 2018 Jun 11];68(6):1322–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27777357
172. Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. Curr Cardiol Rep [Internet]. 2010 Jan [cited 2018 Jun 11];12(1):6–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20425178

APPENDIX A: BARORECEPTOR REFLEX MECHANISM



CO= cardiac output

APPENDIX B: THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)



ACE= angiotensin converting enzyme