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.
ACKNOWLEDGEMENTS

First, I’d like to thank my family and friends, without whom I would not be where I am today. To my parents, for providing their constant support and encouragement that I needed to complete my master’s. To my sister, I have always looked up to you to motivate me to keep working as hard as I can and put in my best effort. I would not have met Jen if it wasn’t for you and owe a lot of my accomplishments to you.

To my amazing lab mates, without you guys, coming into the lab wouldn’t have been half as fun. Arsh, although it was just the two of us in my first year, we quickly became good friends and am grateful to have met you. Thank you for the support, collaboration and laughter (at you). Victoria, I really enjoyed getting to bond with you, and it made poking fun at Arsh more enjoyable.

I would also like to thank Dr. Heather Edgell for all her time and support over the past two years. Finally, I’d like to offer my sincere thanks to my supervisor, Dr. Jennifer Kuk, for taking a chance on me and accepting me into her lab. Thank you for all the hard work, (crazy amount of) patience, and constant guidance these past two years. I very quickly saw that you always want the best for your students, and I am extremely grateful for the opportunities you have provided me. I had an unforgettable experience and have learned so much from you. I hope to have the opportunity to work with you again.
# TABLE OF CONTENTS

ABSTRACT .......................................................................................................................... ii
ACKNOWLEDGEMENTS .................................................................................................... iii
TABLE OF CONTENTS ....................................................................................................... iv
LIST OF TABLES .................................................................................................................. v
LIST OF FIGURES .............................................................................................................. vi
LIST OF ABBREVIATIONS ................................................................................................. vii

1.0 GENERAL INTRODUCTION ......................................................................................... 1

2.0 REVIEW OF RELATED LITERATURE ............................................................................. 3
   Introduction .................................................................................................................. 3
   Hypertension ............................................................................................................... 3
   Regulation of Blood Pressure ..................................................................................... 4
   Obesity Related Health Risks .................................................................................... 7
   Obesity and Hypertension ......................................................................................... 7
   Management of Hypertension in Obesity ................................................................. 8
   Medications available for treatment of Hypertension ............................................. 11
   Medication Dosing in Obesity .................................................................................. 14
   Summary of Literature ............................................................................................ 14

3.0 MANUSCRIPT ............................................................................................................ 16
   Abstract ..................................................................................................................... 16
   Introduction ............................................................................................................... 17
   Methods ..................................................................................................................... 19
      Participants .......................................................................................................... 19
      Survey Methods ................................................................................................... 20
      Prescription Medication Use .............................................................................. 21
      Statistical Analysis .............................................................................................. 22
   Results ....................................................................................................................... 23
   Discussion .................................................................................................................. 26

4.0 GENERAL DISCUSSION ............................................................................................... 31

5.0 REFERENCES ............................................................................................................... 39

APPENDIX A: BARORECEPTOR REFLEX MECHANISM ...................................................... 53
APPENDIX B: THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) .............. 54
LIST OF TABLES

Table 1: Descriptive characteristics of US adults with hypertension by antihypertensive medication type (NHANES 1999-2014).................................................................34

Table 2: Blood pressure differences between users and non-users of individuals on antihypertensive monotherapy by BMI category.........................................................37
LIST OF FIGURES

**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 ...35

**Figure 2:** Mean blood pressures (mmHg) among hypertensive adults using A) ACE Inhibitors and B) ARBs by BMI category and sex.................................................................36

**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.................................................................38
LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-Converting Enzyme</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin Receptor Blocker</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium Channel Blocker</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac Output</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>FPG</td>
<td>Fasting Plasma Glucose</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-Angiotensin-Aldosterone System</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>WC</td>
<td>Waist Circumference</td>
</tr>
</tbody>
</table>
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/m²). BMI can be classified into four categories; underweight, normal weight, overweight, and obesity. Underweight is defined as a BMI < 18.5 kg/m². Normal weight is defined as a BMI
≥ 18.5 kg/m² and BMI < 25 kg/m². Overweight is defined as BMI ≥ 25 kg/m² and BMI < 30 kg/m². Lastly, obesity is defined as a BMI ≥ 30 kg/m² (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 oversecretion 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 ≥ 30 kg/m² 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.
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: \(-14 \pm 1\) mmHg, ARB: \(-16 \pm 1\) mmHg) compared to normal weight individuals (ACE inhibitors: \(-9 \pm 1\) mmHg, ARB: \(-11 \pm 1\) mmHg) \((P<0.05)\). Diastolic BP differences between women ARB users and NoBPMed were also greatest in obesity \((-5 \pm 1\) mmHg) \((P<0.05)\) whilst there were no differences in normal weight individuals \((-1 \pm 1\) 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/m² (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/m²). Participants were categorized as normal weight (18.5 kg/m²≤BMI<25 kg/m²), overweight (25 kg/m²≤BMI<30 kg/m²), or obesity (BMI≥30 kg/m²). 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 \( \beta \)-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 \((-2 \pm 1 \text{ mmHg})\) compared to those with overweight, although minimal \((-1 \pm 1 \text{ mmHg}, P = 0.0198) \). 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: \( P \)
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 \( \beta \)-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).

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>ACE Inhibitors (n=4609)</th>
<th>β-blockers (n=4243)</th>
<th>Diuretics (n=5054)</th>
<th>CCB (n=3387)</th>
<th>ARB (n=2279)</th>
<th>Other (n=974)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.0 (0.3)</td>
<td>61.0 (0.3)*</td>
<td>63.3 (0.3)*</td>
<td>62.4 (0.3)*</td>
<td>63.6 (0.3)*</td>
<td>65.0 (0.4)*</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>45.3 (0.8)</td>
<td>48.0 (0.9)*</td>
<td>53.5 (1.0)*</td>
<td>62.8 (0.8)*</td>
<td>53.4 (1.1)*</td>
<td>57.4 (1.3)*</td>
</tr>
<tr>
<td>Ethnicity (White)</td>
<td>69.0 (1.5)</td>
<td>74.6 (1.3)*</td>
<td>79.3 (1.1)*</td>
<td>74.9 (1.3)*</td>
<td>68.9 (1.6)</td>
<td>73.6 (1.9)*</td>
</tr>
<tr>
<td>Education (HS or more)</td>
<td>79.7 (0.8)</td>
<td>77.3 (1.0)*</td>
<td>78.0 (1.0)</td>
<td>76.1 (0.9)</td>
<td>74.8 (1.0)*</td>
<td>80.7 (1.0)*</td>
</tr>
<tr>
<td>Health Insurance (Insured)</td>
<td>78.8 (0.8)</td>
<td>92.6 (0.5)*</td>
<td>93.8 (0.4)*</td>
<td>93.6 (0.6)*</td>
<td>94.2 (0.5)*</td>
<td>95.0 (0.6)*</td>
</tr>
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<td>Smoking Status (Smoker)</td>
<td>25.3 (0.9)</td>
<td>16.0 (0.7)*</td>
<td>15.2 (0.8)*</td>
<td>12.8 (0.7)*</td>
<td>14.4 (0.9)*</td>
<td>10.4 (0.9)*</td>
</tr>
<tr>
<td>Physical Activity Status (Active)</td>
<td>55.2 (1.0)</td>
<td>46.2 (1.1)*</td>
<td>45.9 (1.1)*</td>
<td>43.9 (1.3)*</td>
<td>45.0 (1.0)*</td>
<td>47.5 (1.7)*</td>
</tr>
</tbody>
</table>

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)*  |
| 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)*  |
| 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)*  |

Blood Pressure (mmHg)

| Systolic                   | 138 (1)                | 130 (1)*           | 132 (1)*           | 131 (1)*     | 135 (1)*     | 133 (1)*     |
| Diastolic                  | 79 (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)*  |
| 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/m²<BMI<25 kg/m²; Overweight=25 kg/m²≤BMI<30 kg/m²; Obesity=BMI≥30 kg/m²; 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.

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

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/m²<BMI<25 kg/m²; Overweight=25 kg/m²≤BMI<30 kg/m²; Obesity=BMI≥30 kg/m²; 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


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#.WekaTVtSyHs


APPENDIX A: BARORECEPTOR REFLEX MECHANISM

CO = cardiac output
APPENDIX B: THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

ACE = angiotensin converting enzyme

* Negative Feedback (to kidney releasing less renin)