HYPERTENSION TREATMENT OPTIONS

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Hypertension is defined as “a systolic blood pressure (SBP) of greater than 140 mm Hg and/or a diastolic blood pressure (DBP) of greater than 90 mm Hg, based on the average of two or more properly measured seated BP readings on each of two or more office visits” (Dunphy, Porter, Winland-Brown & Thomas, 2011, p. 423). The JNC 8 report by James in 2014 added age specific criteria for patients who are ages 60 years old or older with a blood pressure of <150/90, patients ages 30-59 with a diastolic blood pressure <90 with no clear goal of a systolic blood pressure, and ages 30 years and younger <140/90 (James et al., 2014). Hypertension is a health concern that impacts an increasing number of individuals in the United States and worldwide.

The World Health Organization (WHO) states that hypertension is prevalent in approximately 40% of adults age 25 and older with a number worldwide of one billion rising from 600 million in 1980 (World Health Organization [WHO], 2013). Hypertension is a main contributory cause of cardiovascular disease accounting for upwards of 9 million deaths a year worldwide (WHO, 2013).

Hypertension is not a unique disease to any one population, creed, or color. It is an elusive disease, known commonly as the silent killer. This is because patients may go years with the condition without any evident symptoms. Essential Hypertension, which makes up approximately 95% of hypertension diagnoses, is commonly a modifiable disease as its prevalence is directly related to poor diet, lack of exercise, excessive weight, exposure to stressors, use of tobacco, and excessive use of alcohol (WHO, 2013). The remaining 5% of diagnosis of hypertension are from a secondary cause, such as renal disease, sleep problems, diabetes, medications, adrenal problems, thyroid disease, hyperparathyroidism, coarctation of the aorta, obesity, or pregnancy (Warren, R. E. & Padfield, P. L., 2010).

Lastly, the JNC8 breaks down the treatment options of hypertension into non-pharmacological and pharmacological management. Non-pharmacological treatments include lifestyle modification to assist in reaching a normalized blood pressure. Lifestyle modifications with a positive impact on blood pressure include reducing dietary sodium, increased physical activity, weight loss, stress management, reducing alcohol consumption, and smoking cessation (James et al., 2014). Pharmacological treatment includes cautious use of medications (decongestants), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II antagonists, calcium channel blockers (CCBs), diuretics, beta-blockers (BBs), aldosterone receptor blockers (ARBs), alpha-1 blockers, central alpha-2 agonists, direct vasodilators, and combined alpha-and BBs (James et al., 2014).

With the vast options for treating hypertension it is important for providers, including nurse practitioners, to be up to date on the most recent research and guidelines for treating this common diagnosis. Incorporating pharmacological and non-pharmacological approaches to treatment has been shown to have the most positive patient outcomes. Those who are treating patients for hypertension should be knowledgeable of the most up to date treatment guidelines as well as research on treatment options to maximize their patient’s positive treatment outcomes.

**Method**

An extensive literature review was completed via the State University of New York (SUNY) Polytechnic Institute online Cayan library databases. Nursing/medical databases such as CINAHL and MEDLINE were the primary resource of information. The online search was completed with the use of key words, including: “hypertension”, “treatment”, “hypertension treatment”, “ACE inhibitors”, “beta blockers”, “calcium channel blockers”, “complementary and alternative treatments”, and “diuretics”. These key words were used in various combinations to populate search results. Inclusion criterion included peer reviewed articles that were published in the last five years. Articles that were excluded include those that were not written in the English language, those that were not peer-reviewed articles that were published more than five years ago and articles that were not research based.

Additionally, when selecting appropriate articles for review, research studies performed on humans was considered appropriate for the topic. Research results were limited with general search criteria key words like “hypertension treatment.” A larger selection of articles was found by using more specific key search terms as previously mentioned. Further, it is necessary to view the full text of a document. Google scholar was used as a rapid resource to search for the full text format of an article that was found on the Cayan library database search if the full text option was not available through the library website. The search produced over 400 articles combining all results. Literature review in this paper includes 30 articles. (Please refer to Appendix A for literature review grid). Of the articles reviewed, no articles showed one generic treatment option appropriate to treat all patients with hypertension. Research also did not show results for lifestyle modifications and the impact on lowering blood pressure. Many articles suggest lifestyle modification to manage ones hypertension but lacked the supporting data to include these.

**Results**

**Beta-Blockers**

Beta-Blockers are one of the many drug classes used in the treatment of hypertension. Beta-Blockers (BBs) might be the drug of choice for the older, Caucasian hypertensive patient (Wong, 2010). Furthermore, BBs may be used as an add-on drug for patients on antihypertensive medications without adequate control (Bakris et al., 2010; Neutel, Smith & Gradman, 2010; Turner et al., 2010; Weber et al., 2012; Wong, 2010). Nebivolol hydrochloride, a beta-blocker, was shown to reduce blood pressure in hypertensive patients when prescribed as an add-on therapy for patients diagnosed with stage I or stage II hypertension. Additionally, it was shown to be well tolerated with minimal side effects in the sample population (Neutel, Smith & Gradman, 2010). In this study, Neutel, Smith & Gradman (2010) evaluated only 669 patients in their double-blind, placebo-controlled, parallel group study. Thus, their work was limited with a small sample size. However, they studied patients over the age of 18 who had inadequate control over their blood pressure on their current medication regimens.

Beta-blockers are frequently used in conjunction with ACE inhibitors to reduce blood pressure (Bakris et al, 2010; Weber et al., 2012). Weber et al. (2012) showed how the addition of nebivolol to lisinopril in patients with stage II hypertension added to the effectiveness of blood pressure reduction to achieve target blood pressure goals in the sample population of patients. The combination therapy of two drugs was well tolerated and more effective than either drug used alone in monotherapy for antihypertensive therapy. “This study has demonstrated that the B-blocker nebivolol adds significantly to the DBP-reducing effect of the ACE inhibitor Lisinopril in patients with stage 2 hypertension. Specifically, this combination therapy was significantly more effective than nebivolol alone and Lisinopril alone in producing this effect.” (Weber et al., 2012, p.591). In this study, Weber et al. examined patients with a double-blind, placebo-controlled parallel group trial. They looked at patients with stage 2 diastolic hypertension who were between the ages of 18-64. Because of this sample size, the study is limited as it did not include the elderly. The elderly population accounts for a large number of patients who are treated for hypertension. Additional limitations to this study include an unexpected finding of a placebo effect on blood pressure. Large portions of the sample size, one third, were African Americans. Lastly, the maximum dose of nebivolol-hydrochloride was not used in the study. This study should be reproduced with a larger sample size, including other ages as well as a variety of races within the sample (2012).

Carvedilol, another common beta-blocker, was studied with Lisinopril, a common ACEI to determine if starting patients on combination therapy with two drugs was more beneficial than monotherapy initiation with add-on therapy using 15 groups of varied dosing levels. There was no benefit to starting therapy with any one of the combinations of the two drugs. Yet, high doses of combination groups in the sample population did show a significant reduction in blood pressure as compared to high dose monotherapy groups (Bakris et al., 2010). Within the sample of patients studied, Bakris et al. looked at men and non-pregnant females over 18 years old. Patients who were taking three or more antihypertensive medications were excluded from the sample. The study looked at patients from 172 various clinical sites and included 654 persons. Within this sample, patients were placed into one of fifteen different arms of the study randomly. Patients were given carvedilol CR at a dose of 20, 40 or 80mg or Lisinopril 10, 20, or 40mg. Another set of patients were given one of the 9 different combinations of these medications/dosages. This was done in a randomized, double-blind factorial design manner. The study was limited as it had so many arms of the study, that each arm included 35-45 patients in each arm. The sample included only 5% of participants of non-white or African American race. The study should be replicated with more persons in each arm of the study and include a variety of races within the sample population (Bakris et al., 2010).

Plasma renin activity may predict the patient response to antihypertensive treatment with beta-blockers (Turner, et al. 2010). This prediction is used for both add-on therapy as well as single medication therapy known as monotherapy. Turner et al. (2010) randomly assigned patients to take hydrochlorothiazide or atenolol as initial therapy and if necessary, used the alternate medication as add-on therapy. Response rates were predicted using plasma renin activity. Higher plasma renin activity was a predictor of greater responses to both mono- and add-on therapy with atenolol and a lesser response was seen with hydrochlorothiazide, a thiazide diuretic. Thus, the plasma renin activity is a better benchmark to predict responses with beta-blockers (Turner et al., 2010). Turner et al. examined 363 patients under the age of 65 years old using objectives and design of PEAR study. The patients were randomly assigned to take hydrochlorothiazide then atenolol or atenolol then hydrochlorothiazide. Patients monitored their blood pressures at home and were used to monitor their response to therapy. Age and race were used to renin profile patients. This study was limited to the size of the sample and the exclusion of elderly from the study. Additionally, blood pressures were monitored by patients in their own homes and could be inaccurate readings (Turner et al., 2010).

**Pharmacological**

Angiotensin converting enzyme inhibitors (ACEI) and calcium channel blockers (CCB) were found fairly comparable to the commonly used thiazide diuretics and B-blocker combination, despite some evidence which showed the possibility of a lower efficacy of the B-blockers (BB) (Wong, 2010). Add on therapy is recognized to be a proxy measure of drug efficacy (Wong, 2010). Add-on therapy is utilized when a patient does not show effective blood pressure lowering effect with his or her current medication regimen and another prescription is added (Bakris et al, 2010; Neutel, Smith & Gradman, 2010; Turner et al., 2010; Weber et al., 2012; Williams et al., 2015; Wong, 2010). Wong suggests that the rate of add-on therapy tends to be a factor that influences those who prescribe medications, more so than adverse drug reactions when starting antihypertensive therapy for patients (2010).

Wong (2010) used a cohort study in Hong Kong and studied patients who were prescribed antihypertensive drugs for the first time in two different primary care offices. This covered a large sample size of 2531 and found that the incidence of add-on therapy with ACEIs was the highest among both young females and elderly females when compared to other drug classes. The rate of add-on therapy for ACEIs in young women was found to be 31.1% in comparison to thiazide diuretics (9.9%), beta-blockers (12.9%) and CCBs (9.6%). ACEIs in elderly women as an add-on, was noted at a rate of 18.0%, the highest percentage of all of the classes compared. Young males and elderly males also had the highest add-on rates for ACEIs with 20.3% and 12.5% respectively. Thiazide diuretics, BBs and CCBs had similar add-on rates throughout genders and ages. Although, add-on therapy is common across all drug classes, the rate is significantly higher with ACEIs. In the male population, both young and elderly, add-on therapy was highest with ACEIs than other drug classes, yet there was no statistical significance. Special consideration should be made when understanding this study was done on all Asian patients. As it has been determined that CCB’s are most effective in black patients, ACEIs are most effective in younger white patients and BBs most effective in older whites. Therefore, the results of this study may represent pharmacokinetics related to race (Wong, 2010). Limitations to Wong’s study include only two primary care offices were examined in Hong Kong and other races/ethnicities should have been included (Wong, 2010).

Not only does the medication, itself, impact how well blood pressure is controlled, but the way the medication is taken may also impact blood pressure reduction. (Hermida, Ayala, Mojon & Fernandez, 2011 and Grimmsman & Himmel, 2011). Grimmsman and Himmel (2011) studied the utilization of antihypertensive medications by patients by performing their study at pharmacies dispensing medications. By doing so they, “summed the doses of all dispensed drugs. The researchers calculated the PDD (= total dose divided by the number of days) that they then expressed as the PDD:DDD ratio (= amount of DDD per day and person.) (Grimmsmann & Himmel, 2011). They evaluated the continuous prescriptions for thiazide-diuretics, beta-blockers, dihydropyridine, calcium channel blockers, ACE inhibitors, and ARBs. The ratio for beta-blockers = 0.94, the ratio for ARBS = 1.88 and lastly, the ratio for ACE inhibitors = 2.17. Overall, it was found that the differences between defined daily dosing and prescribed daily dosing were related to drug classes and not a matter of patient characteristics (Grimmsmann & Himmel, 2011). Their study was limited by relying on patients actually filling their prescriptions. An impressively large sample of 149,704 was able to be studied with this observational study method (Grimmsmann & Himmel, 2011).

Additionally, it is thought that some drug resistant hypertension may be related to an increase in sodium retention. Therefore, Williams, et al. (2015) tested their theory that patients with drug resistant hypertension may respond better to spironolactone rather than any other add-on therapy which were non-diuretic in nature: bisoprostol, doxazosin, and a placebo. This was done in a small sample size of 335. Of this sample population, 285 patients took spironolactone, 282 took doxazosin, 285 took bisoprostol and 274 took the placebo.  Only 230 patients completed all of the four treatment cycles to compare treatment options. Spironolactone was superior to the placebo and most effective of the add-on drugs tested. Thus, the hypothesis of sodium retention related to the condition was supported by their findings (Williams et al., 2015).

In addition to high blood pressure reduction, management of hypertension also includes the reduction of an individual’s cardiovascular risk (Hermida, Ayala, Mojon & Fernandez, 2011; Mortsiefer et al., 2015). Cardiovascular risks include various cardiovascular events like: death, myocardial infarction (MI), angina, revascularization, heart failure, arterial occlusions and stroke. These are major health concerns potential for patients with hypertension. It was found that patients who took their antihypertensive medication at bedtime showed a decrease in possible risks of death, MI and stroke (Hermida, Ayala, Mojon & Fernandez, 2011). Mortsiefer et al. (2015) examined the impact of utilizing complex interventions compared to using simple interventions to reduce cardiovascular risk in 3443 hypertensive patients using a prospective non-blinded longitudinal cluster-randomized controlled trial.  Offices were assigned complex vs. simple interventions randomly for their patients.  Data was first collected at baseline and then again at 6-9 months after the interventions. The simple interventions closely resembled typical care of primary care providers. Overall, it was found that complex intervention, which included clinical outreach, written materials, personal intervention and phone calls did not yield higher reduction of cardiovascular risks when compared to simple interventions (Mortsiefer et al., 2015). Limitations of the study performed by Mortsiefer et al. (2015) included insufficient interventions, too short of a follow up period, and patient noncompliance.

Taking this a step further, Hermida, Awala, Mojon and Fernandez (2011) examined the timing of dosing of antihypertensive medications and if there was a reduction in the cardiovascular risk related to the same. A sample size of 661 was studied using an open-label trial. They excluded patients who were working night shifts, pregnant and those with major cardiovascular disorders. Patients in the sample were randomly selected to take their antihypertensive medications in the morning or at bedtime. Urine and blood samples were collected as well as serial blood pressure readings for 48 hours. Bedtime dosing also improved control of blood pressure during waking/ambulatory hours and on average, a lower blood pressure during hours of sleep. As determined, those were studied and taking at least one blood pressure lowering medication at bedtime had a cardiovascular risk of one third of that of those who took their medications upon awakening in the morning (Hermida, Ayala, Mojon & Fernandez, 2011). All antihypertensive drugs studied by Hermidia, Ayala, Mojon & Fernandez were not listed, but specifically mentioned ACE inhibitors and ARBs (2011). Another limitation of this study is the exclusion of various patients from the study. These patients have various diagnosis that account for a large percentage of those whom are routinely treated for hypertension including: pregnant patients, drug users, ETOH abuse, CVD disorders, AIDS, night shift workers, secondary hypertension, type 1 diabetes and kidney failure (Hermida, Ayala, Mojon & Fernandez, 2011).

**Non-Pharmacological**

In addition to pharmacological methods to reduce blood pressure in hypertensive patients, complementary and alternative therapies may be used to help in the reduction of both systolic and diastolic blood pressure. One of the most documented complementary treatments for hypertension patients is acupuncture (Cevik & Iseri, 2013 & Li et al., 2014). Both studies, Cevik & Iseri (2013) and Li et al. (2014) demonstrated the positive effect of acupuncture on blood pressure reduction. The study compared acupuncture treatment with sham-acupuncture treatment, which is a more invasive form of acupuncture. Through this research, it was shown that acupuncture in conjunction with antihypertensive medications lower blood pressure better than with medication alone. A sample of 223 patients using acupuncture and 163 using sham-acupuncture were studied. Findings did not support the use of acupuncture alone to reduce blood pressure in hypertensive patients. Thus, acupuncture alone is not sufficient to reduce a hypertensive patient’s blood pressure (Li et al., 2014). Similar studies should be replicated with larger sample sizes (Li et al., 2014).

Overall, using acupuncture with antihypertensive medications had a result of lowering blood pressure for hypertensive persons (Cevik & Iseri, 2013 & Li et al., 2014). Cevik & Iseri studied patients who initially established for acupuncture treatment of back pain. Incidentally, they were found to have been treated for over 2 years, for hypertension, by a cardiologist. This was a very small sample size of 35 patients, which also serves as a limitation to the study. Males in the population were between the ages of 15-59 and females ages ranged from 43-80. Of the patients who were on antihypertensive medications, the following medications were used and the effect enhanced by the use of acupuncture: beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and diuretics (Li et al., 2014). Whereas, Cevik reports patients were on 1-3 antihypertensive drugs including: ACE inhibitors, diuretics and beta-blockers (2013).

Further, the research of Cevik & Iseri (2013) documents that acupuncture also has a positive effect on reducing the unwanted side effects of antihypertensive medications. The most common side effects reported by patients in this study included: headache, fatigue, joint pain, dizziness, weakness, sleep disturbances, edema, depression, cold hands/feet and back pain (Cevik & Iseri, 2013). Out of these, back pain and headache were the most common reasons that patients sought out acupuncture therapy (Cevik & Iseri, 2013).

**Sodium and Hypertension**

Pimenta et al. (2009) conducted a randomized crossover study aimed at determining whether sodium consumption had a direct effect on the treatment of resistant hypertension. Twelve total subjects, with resistant hypertension defined as a blood pressure of greater than 140/90, completed the study in which a specific salt regimen was followed a total of four weeks (Pimenta et al., 2009). Week one, a high diet salt was consumed followed by a two-week regular diet, and concluded with one week of a low salt diet (Pimenta et al., 2009). Blood pressure readings during week one and week four were taken via office visits and ambulatory blood pressure measurements (ABPM) with a reduction noted in the low salt week (Pimenta et al., 2009). Statistical significance was reached with ABPM and office readings showing that excessive sodium in the diet contributes to resistance to hypertension treatment (Pimenta et al., 2009). Despite the statistical significance this particular study lacks a large and diverse sample size, which leaves much to be determined regarding the role of sodium in a greater population. Additionally all participants in this study are taking three or more antihypertensives including a thiazide, leaving a gap in what effect sodium reduction would have on patients with less than three or no antihypertensive agents.

Slagman et al. (2011) conducted a multi-center crossover, randomized controlled trial among 52 patients with non-diabetic nephropathy to determine the effects that sodium has on blood pressure reduction. Patients excluded were those with diabetes mellitus, having renal-vascular hypertension, those that had a cardiovascular event in the previous six months, those immunosuppressed, or those that use NSAIDs (Slagman et al., 2011). The intervention group consumed a low sodium diet in conjunction with standard medications with and without an angiotensin converting enzyme (ACE) inhibitor, while the control had a regular diet with standard medications with and without an ACE inhibitor (Slagman et al., 2011). Blood pressure monitoring showed a statistical significance in the reduction of blood pressure for patients with a low sodium diet, significantly larger than the reduction with an angiotensin receptor blockade (Slagman et al., 2011). This particular study adds to the existing literature regarding dietary sodium reduction and improved blood pressure control despite having a small population size with short-term data (Slagman et al., 2011). Additionally limitations include no hard end points and limited generalizability of data as a result of the exclusion criteria utilized (Slagman et al., 2011).

Pimenta et al. (2009) and Slagman et al. (2011) both served to demonstrate the statistical significance of blood pressure control with simple dietary changes, specifically with reduction of sodium intake. Based on the results of these two studies, sodium reduction is a significant factor that must be utilized in the management of hypertension, specifically in patients whom are resistant to standard treatment measures. Despite the promising results, a major gap exists in whether sodium reduction is beneficial, and in what degree in the pre-hypertensive patient.

**Baroreceptor Control Treatment**

Scheffers et al. (2010) investigated the functionality of the Rheas device, utilized to stimulate baroreceptors, to reduce blood pressure. They conducted a prospective, nonrandomized feasibility study among 45 patients ages 21 and older with blood pressure readings greater than or equal to 160/90 while already on three anti-hypertensives including a diuretic (Scheffers et al., 2010). Twenty-six subjects completed the full duration of the study, which consisted of device activation one month following implantation to help manage high blood pressures (Scheffers et al., 2010). All reductions in blood pressure were statistically significant, aside from a measurement error that was found at three months, showing a meaningful reduction in those whom were difficult to manage with medications alone (Scheffers et al., 2010). Limitations included high number of patients dropping out due to safety concerns, and exclusion criteria leading to a small population size (Scheffers et al., 2010).

Further research conducted by Bisognano et al. (2011) regarding baroreceptor activation, to lower blood pressure, helped to support the statistical significance it holds. Two hundred sixty-five patients with blood pressures greater than or equal to 160/90 currently being treated with at least three antihypertensives including a diuretic were included in this particular trial. All 265 were implanted with a baroreceptor-activating device with 181 receiving the therapy for a full 12 months and 84 receiving therapy for the final 6 months only. Blood pressures were significantly reduced at six months and 12 months in all patients with baroreceptor activation, P =< 0.001, however safety ends points were not met (Bisognano et al., 2010). Limitations to this study are the safety concerns with device implantation and medication changes were allowed to be made during the study period (Bisognano et al., 2011). Although this device is promising in treatment of resistant hypertension, there are significant safety concerns that it’s implantation holds making more research necessary to determine what safety measures may be necessary.

Scheffers et al. (2010) and Bisognano et al. (2011) independently showed the effectiveness of baroreceptor devices in resistant hypertension. Although baroreceptor control in the treatment of resistant hypertension has proven an effective treatment modality, there is a significant concern of safety risks with device implantation. This concern is something that must be further investigated prior to the established use of devices, such as the Rheos, within a specific population of patients showing resistance to various other hypertension treatment modalities.

**Resistant Hypertension**

Dimeo et al. (2012) conducted a parallel group, randomized controlled trial in which 50 participants from a hypertension clinic with a blood pressure greater than or equal to 140/90 were enrolled. Of these individuals, all were on a minimum of three antihypertensive agents with 26 participating in a structured treadmill exercise program three times a week ranging from 8 to 12 weeks long (Dimeo et al., 2012). Twenty-four patients did not participate in the structured exercise program and were included in 24 hour blood pressure monitoring similar to the intervention group (Dimeo et al, 2012). Statistical significance in blood pressure reduction was reached, P = 0.03, with aerobic exercise in resistant hypertension indicating that a low responsiveness to antihypertensive drug therapy does not mean a low responsiveness to exercise (Dimeo et al., 2012). A limitation to this particular study is a small sample size and geographical differences. These results show clear evidence of the effects a structured exercise program has on difficult to control hypertension. Patients that are able to exercise should be educated on its benefits and encouraged to adapt it into their lifestyle as an effective treatment measure. Further data collected should focus on whether exercise programs used with patients on less than three antihypertensive medications would have positive outcomes.

Heshka, Ruzicka, Hiremath, & McCormick (2010) conducted a retrospective cohort design in which 88 renal patients from a clinic at the Ottawa Hospital were included. Thirty-four patients with chronic kidney disease (CKD) and fifty-four patients in the absence of CKD were given low dose spironolactone to determine effects it would have in the presence of kidney disease (Heshka et al., 2010). Statistical significance was found in CKD patients, P = 0.006, with a reduction in difficult to control blood pressure (Heshka et al., 2010). Limitations in this study include small population, not a controlled trial and limitation to one particular geographical area.

Vaclavik et al. (2011) conducted research that supports the use of spironolactone in treatment resistant hypertension, although not specifically for patients with CKD. A total of 117 patients were enrolled in a double blind, placebo-controlled multi-center trial with blood pressures greater than 140/90 despite three antihypertensives along with a diuretic being part of their initial treatment (Vaclavik et al., 2011). Fifty-nine patient received spironolactone as an add-on therapy while fifty-eight received a placebo (Vaclavik et al., 2011). Systolic blood pressure reduction was statistically significant, P = 0.024, pointing to the added benefit of adding spironolactone as a treatment modality in resistant hypertension (Vaclavik et al., 2011). Limitations of this study include a small sample size despite a recruitment effort aiming at 300 patients.

Spironolactone has been shown to be effective in assisting with blood pressure reduction when added into medication therapy (Heshka et al., 2010; Vaclavik et al., 2011 & Williams et al., 2015). Heshka et al. (2010) and Vaclavik et al. (2011) showed the effectiveness that low dose spironolactone has when added to standard hypertension treatment of three medications, one of which being a diuretic. When options such as exercise, diet, and medication reactions/resistance do not allow for optimal treatment, the addition of spironolactone gives an added option for providers.

Muntner et al. (2010) performed a cross-sectional analysis of 3612 patients from the CRIC (Chronic renal insufficiency cohort) study and determined that the prevalence of hypertension in these patients is about 85.7% with 98.9% of these patients being aware of this particular diagnosis. Despite this knowledge, 67.1% and 46.1% had hypertension controlled to less than 140/90 and 130/80 respectively (Muntner et al., 2010). This particular information has shown a significant effect on the focus of hypertension treatment as a large number of these particular patients have not reaching 100% treatment goals for a variety of reasons. Better control of blood pressure was noted with younger and non-black patients, while hypertension being more common in higher BMI, current and former smokers, with diabetes, and cardiovascular disease (Muntner et al., 2010). Blood pressure control was best with patients being treated with angiotensin receptor blockers and ACE inhibitors versus other medications such as diuretics, beta-blockers, and calcium channel blockers (Mutner et al., 2010). This research leaves a major gap in the knowledge that providers must pass onto their patients in an effort to reduce the percentage of poorly controlled hypertension. Treatment must specifically focus on proper adherence to prescribed treatment modalities as described within this paper.

Weber et al. (2009) performed a randomized double-blind study with 379 patients receiving at least three antihypertensive medications including a diuretic. They determined a medication called darusentan, a selective endothelin-receptor antagonist, allows for further blood pressure reduction in patients with persistent treatment resistant hypertension (Weber et al., 2009). The medication was used for fourteen weeks in a total of 247 patients at three various doses, with a placebo control group of 132 patients (Weber et al., 2009). The results were statistically significant in the reduction of blood pressure with all doses, allowing this particular medication to be used as an addition to patients with treatment resistant hypertension.

**African-American Specific**

One major population that statistically has higher incidences of hypertension is African Americans. A study by Brewster and Seedat (2013) suggests that clinicians treat individually of African ancestry; however they looked at why patients with African ancestry respond differently to different anti-hypertensive medications like β**-**blockers and those medications that inhibit the renin-angiotensin system. The researchers used systematic reviews to search the literature for studies that could explain why hypertensive patients with African ancestry respond differently to anti-hypertensive medications.

Brewster and Seedat (2013) retrieved 3,763 papers and 72 reports that looked at major classes of antihypertensive medications, calcium channel blockers, diuretics, renin-angiotensin system interference drugs, and beta-blockers. It was concluded that the current data they found was inconclusive in regards to why patients with African ancestry respond atypically to antihypertensive medications (Brewster & Seedat, 2013). They were not able to find any evidence of a biochemical or pharmacogenomics parameter that could predict one’s response to antihypertensive medications; instead one’s self-defined African ancestry was the best way to predict one’s response to antihypertensive medications (Brewster & Seedat, 2013).

Additional research by Lee et al. (2011) looked at the relationship between β1-adrenergic receptor blockers (ADRB1) polymorphisms and the response on blood pressure to β-blocker metoprolol treatment amongst African American patients with early hypertensive nephrosclerosis (Lee et al., 2011). Researchers selected participants from the African-American study of kidney disease (AASK), 1,094 African American men diagnosed with hypertensive nephrosclerosis that were randomized to metoprolol [329] (Lee et al., 2011). They then analyzed two different nonsynonymous ADRB1 polymorphisms, Ser49Gly and Gly389Arg among the participants (Lee et al., 2011).

Within the study, of the 329 selected to be on metoprolol, 96% were genotyped with Ser49Gly and 94% were genotyped Arg389Gly (Lee et al., 2011). The research found that the genetic marker Ser49Gly was predictive of response to metoprolol with those patients with a BMI of 39 or greater with that group achieving the target MAP (mean arterial pressure) of 107 mm Hg by 32% (Lee et al., 2011). There was also a positive correlation of the Arg389 obese genetic carriers, showing a 32% faster rate to reach the target MAP (Lee et al., 2011). The individuals that were genotyped Arg389 were less responsive to β-blockers, in contrast to other studies that showed a short-term response to beta-blockers, over a one-year period (Lee et al., 2011)

**Renal Denervation**

Another treatment for hypertension that has shown significant reduction in blood pressure is renal sympathetic denervation, usually designated for patients who are resistant to drug therapy (Krum et al., 2011). The procedure involves an endovascular catheter approach aimed at disrupting the renal sympathetic nerve utilizing radio-frequency ablation through an electrode at the tip of the catheter (Krum et al., 2011). Krum et al performed a study and treated 153 patients with a catheter based denervation procedure (Krum et al., 2011). They found that 92% of the patients had a blood pressure reduction of 10 or more mm Hg (Krum et al., 2011). The reduction in blood pressure was significant with the exception of the 24-month diastolic data (Krum et al, 2011). This study showed great success with this procedure however, the authors point out that there is a substantial question that remains which is, is this procedure durable as sympathetic nerves tend to regrow after being damaged (Krum et al., 2011). The limitations cited by Krum et al. (2011) is that there was no control group with which to make comparisons regarding blood pressure and eGFR responses over time.

A second study looked at renal denervation in a patient group that was resistant to medication management, on three or more anti-hypertension medications. It was found that the procedure could be safely used to substantially reduce blood pressure in this population (Esler et al., 2010). Researchers found on average a reduction of 32/12 mm Hg in the renal denervation group compared to no change in the control group (Esler et al., 2010). One limitation of this study conducted in 24 treatment centers throughout Europe, Australia, and New Zealand was that the patients recorded their own blood pressure and drug compliance at home (Esler et al., 2010).

The study by Esler et al. (2010) involved a catheterization with the Symplicity catheter, which was advanced into the renal artery where a radiofrequency (RF) generator applied low power RF between four-six times along the length of the renal artery (Esler et al., 2010). Again, this procedure showed promising results for patients with medication resistant hypertension. This study showed an 84% success rate in patients of 10 or more mm Hg with no major adverse effects from the procedure (Esler et al., 2010). An important piece of information from this study is the researchers followed patients receiving renal denervation GFR which showed no evidence of worsening renal functions, suggestive that renal denervation therapy is safe even for patients with mild-to-moderately impaired renal function (Esler et al., 2010). The limitation noted in Esler et al. (2010) was the small sample size.

**Hypertension in the Elderly**

Several studies have looked at hypertension treatment in adults in their fifties and sixties, some suggesting that hypertension treatment in very old adults (aged over eighty years of age) could be less effective or even harmful (Mukhtar & Jackson, 2012). As a result of this thought and a need to prove the hypothesis either negative or positive, the Hypertension in the Very Elderly Trial (HYVET) was launched and a double-blind placebo-controlled trial involving the data from 3845 older adults from 13 countries (Mukhtar & Jackson, 2012). Researchers grouped the participants into two categories, one with indapamide 15mg sustained release (a thiazide like diuretic) and a matching placebo group (Mukhtar & Jackson, 2012).

Research results showed significant evidence that anti-hypertensive treatment with sustained release indapamide in octogenarians is helpful (Mukhtar & Jackson, 2012). One criticism of this study was that a majority of the recruited participants were from Eastern Europe and China where there is an increased prevalence of cerebrovascular events compared to patients in Western Europe (Mukhtar & Jackson, 2012). Despite these limitations, the HYVET study showed that anti-hypertensive therapy reduced all-cause mortality and a large reduction in heart failure (Mukhtar & Jackson, 2012). Limitations cited by Mukhtar & Jackson (2012) were that the participants were mainly patients from Eastern Europe and China where there is an increased prevalence of cerebrovascular events compared to patients in Western Europe, as well as four of the centers included in the study closed within the first year.

Welsh et al. performed a meta-analysis review to look at the prevalence of hypertension in patients who reside in long term care facilities and the treatment over time (Welsh et al., 2014). They reviewed over six thousand initial articles and whittled down to 16 articles that met their eligibility criteria (Welsh et al., 2014). The findings of their research showed that despite increasing usage of antihypertensive agents in long term care patients; there was no measurable improvement in blood pressure control (Welsh et al., 2014). This raised the question; is this vulnerable patient population being unnecessarily exposed to a treatment that can cause significant side effects (Welsh et al., 2014)? The findings certainly justify further exploration of reasonable treatment options for patients who reside in long term care facilities (Welsh et al., 2014). Limitations noted by Welsh et al. (2014) included that there were a very low number of articles that qualified for the study.

Moreover, a German study also looked at hypertensive management between elderly patients in nursing homes compared to those living at home (Lochner et al, 2011). This researcher group performed a retrospective, cross-sectional, pharmacoepidemiological study of patients aged 65 or older with a diagnosis of arterial hypertension (Lochner et al, 2011). They analyzed a total number of 508 subjects split equally between those residing in nursing homes and those living in their own homes in the community with a median age of 80.4 years of age (Lochner et al., 2011).

Lochner et al. (2011) yielded results showing that nursing home patients had better control of blood pressure (61% vs. 48.1% with a p=0.015) (Lochner et al., 2011). The community dwelling population showed less control while receiving more hypertensive medications compared to the nursing home group (Lochner et al., 2011). Given this information, there was also a finding that nursing home patients received unnecessary medications, like tranquilizers, than those in community dwelling patients (Lochner et al., 2011). Limitations noted by Lochner et al. (2011) were that the information from the community dwelling patients was self-reported.

**Sleep and Hypertension in Female Patients**

Sleep is an integral part in maintaining a healthy life. It is no shock that lack of quality sleep may cause health implications like hypertension. A study looked at sleep patterns of women that were involved in the Nurses’ Health Study I (1986 & 2000) and II (2001) and their self-report of sleep (Gangwisch et al., 2013). The researchers analyzed over 235,000 participants in the Nurses’ Health study and found that those that reported five or less hours of sleep per night had a higher prevalence of hypertension compared to those who self-reported seven or more hours of sleep, especially amongst younger women aged 50 or younger (Gangwisch et al., 2013). The data was not supportive of a higher incidence of hypertension in women aged 60 or greater (Gangwisch et al., 2013). Findings were slightly mediated by obesity but a correlation could not be confirmed with diabetes, shift work, snoring, menopause, postmenopausal hormone therapy, or high cholesterol (Gangwisch et al., 2013). This study lends support to the hypothesis of shorter sleep cycles may play a role in the etiology of hypertension in younger women (Gangwisch et al., 2013). Limitations cited by Gangwisch et al. (2013) were that the information was self-reported, leaving much room for error.

Stranges et al. performed a population-based study that also provides supportive data to support that shorter sleep durations are contributory to hypertension with a higher incidence noted in women compared to that in men (Stranges et al., 2010). They examined a cross-sectional gender based association of sleep duration and hypertension from participants of the Western New York Health Study (1996-2001) (Stranges et al, 2010). They defined hypertension as ≥140/≥90 or those individuals whom regularly took antihypertensive medications (Stranges et al., 2010). Their findings again found that a shorter sleep cycle was contributory to hypertension amongst women compared to those who slept between 6-8 hours a night (Stranges et al., 2010). The women affected were also pre-menopausal and there was no association among men either (Stranges et al., 2010). Limitations noted by Stranges et al. (2010) were that the information was self-reported and that the primary participants were white collar, Caucasians, limiting the generality of the study.

**Intensive Management**

A prospective, multi-site cluster randomized pragmatic trial conducted by Heisler et al looked at improving blood pressure control among patients diagnosed with diabetes in 3 Veterans Affairs and 2 Kaiser Permanente health centers, both considered high-performing (Heisler et al., 2012). This group utilized pharmacists, armed with evidenced-based algorithms and state-of-the-art tools to improve integrated delivery of health care to improve blood pressure control among diabetic patients (Heisler et al, 2012). The study found that those patients selected for the intensive adherence and medication program did more rapidly lower systolic blood pressures (SBP) but the “usual-care” patients achieved the same SBP levels at the six-month post intervention period (Heisler et al., 2012). This study served to prove that efficacy trials are best tested in a small program before a widespread adoption, as this trial did not prove effective (Heisler et al., 2012). A limitation noted by Heisler et al. (2012) was that despite efforts to ensure standardization, it was difficult to guarantee with the number of pharmacists involved in the study.

Another randomized trial looked at intensive control measures versus standard blood pressure control. A study by Wright et al. (2015) looked at 9361 patients with a systolic blood pressure of 130 mm Hg or higher and risk factors for cardiovascular disease, with the exception of diabetes. The target systolic blood pressure was set to 120 mm Hg for the intensive group compared to 140 mm Hg for the group to reach standard control measures (Wright et al., 2015). The goal number was changed in this study with the hope of significantly changing risks for certain cardiovascular events (Wright et al., 2015).

The group of patients whose goal SBP was 120 mm Hg, compared to the standard 140 mm Hg, resulted in statistically less rates of fatal and nonfatal cardiovascular events and any cause death (Wright et al., 2015). This accounted for a 43% lower risk of death in the intensive intervention group of patients (Wright et al., 2015). It was noted, however, that there were more instances of serious adverse events in the intensive group (Wright et al., 2015). This includes hypotension, syncope, electrolyte abnormalities, and acute kidney injury/failure (Wright et al., 2015). Limitations cited by Wright et al. (2015) were the length of the study and the high number of participants.

**Conclusion**

Hypertension is a common healthcare concern throughout the United States as well as the world. Hypertension may be primary in nature, without another cause; Secondary hypertension, which is caused by another health issue; and white coat syndrome, which is experienced in the health care setting, but not true hypertension, as these patients will have normalized blood pressures at home. Primary and secondary hypertension requires management from healthcare providers, like nurse practitioners. Furthermore, given the described neural pathophysiology of primary (essential) hypertension; renal denervation confirms the crucial relevance of renal nerves in elevated blood pressure seen in patients (Esler et al., 2010).

The treatment of hypertension can be challenging for providers and patients alike. There is a wide array of medications to consider when considering prescribing antihypertensive drugs to a patient meeting the diagnostic criteria for hypertension. Treatment options are continuously expanding and research on treatment options continues to take place. It is recommended that clinicians, including nurse practitioners, adhere to the guidelines set by the JNC8 at the present time (James et al., 2014). To date, there are multiple drug classes of antihypertensive medications as well as complementary and alternative treatments. Patients are almost always encouraged to modify their lifestyle in ways that would benefit their medical condition and thus decrease their blood pressure. These modifications enhance the effectiveness of pharmacological treatment, and include things such as sodium reduction, exercise programs, and acupuncture.

Not only is it of paramount importance to reduce blood pressure to a normalized level, but also it is also essential to reduce the cardiovascular risk of patients. This, in turn, reduces the possibility of severe issues like cardiovascular death, myocardial infarction and stroke. The reduction of the cardiovascular risk of a patient will have an impact on the overall health of the hypertensive patient. The current research that is available does not suggest a cookie cutter type approach to management of hypertension. There is positive research to suggest all antihypertensive medication classes have positive effect on blood pressure reduction, both systolic and diastolic.

Additionally, providers should take into account that each patient is different. Appropriate lifestyle modifications should be encouraged including: diet management, the reduction of salt intake, weight management/loss, exercise, smoking cessation, as well as control of other comorbidities including high cholesterol. In conjunction with lifestyle modifications, the provider should evaluate the patient’s race, age and gender to help determine which antihypertensive medication to initiate. Various classes of antihypertensive drugs have proved to be more effective in different age brackets and races. The same goes for male versus female.

Overall, the trend among research shows that it usually takes a combined treatment approach to effectively reduce blood pressure in hypertensive patients to an acceptable range. Monotherapy, although sometimes effective, often times do not sufficiently reduce blood pressure. By utilizing treatment standards and guidelines set forth by the JNC8 in conjunction with the knowledge base from the most up to date research, efforts can be made to reduce the number of medications patients take to maintain adequate blood pressure control (James et al., 2014). Advances in medications have created combination pills with more than one drug, which generally work well together, to help assist in this process.

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**Appendix A**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Population, Demographics, Sample Size, Setting, Timing** | **Intervention** | **Comparative group/control** | **Outcome/Findings <0.05 is good** | **Methodology/Type of study** | **Results** | **Limitations** |
| Bakris, G. K., Lyengar, M., Lukas, M. A., Ordronneau, P., &Weber, M. A., (2010). Effects of combining extended-release carvedilol and lisinopril in hypertension: Results of the COSMOS study. *The Journal of Clinical Hypertension, 12*(9), 678-686. | Men and nonpregnant females over 18 years of age.  Patients taking three or more antihypertensives were exvluded.  At 172 clinical sites. N=654. | Patients were randomly placed into one of 15 arms of the stydy.  A dose of carvedilol CR (20, 40 or 80mg) or lisinopril  (10, 20, or 40mg).  There were also patients with one of the 9 varried combinations of these drugs/dosing. | Fifteen different groups of patients studied. | Not available | Randomized, double-blind, factorial design trial. | Did not demonstrate the superiority of one of the combinations of medication doses tested.  Combination therapy was well tolerated.  High dose combination groups did show a significant reduction in blood pressure as compared to high dose monotherapy groups. | Only 5% of participants were of non white/Arican American races.  Only testing patients in stage 1 or stage 2 hypertension.  35-45 people in each arm of the study. |
| Bisognano, J. D., Bakris, G., Nadim M. K., Sanchez, L., Kroon A. A., Schafer, J., Leeuw, P. W., & Sica, D. A., (2011). Barreflex activation therapy lowers blood pressure in patients with resistant hypertension. *Journal of the American College of Cardiology, 58*(7), 765-773. | 265 patients with at least 1 out-patient, in-office, SBP >= 160 and DBP >= 80 mm Hg. with at least 3 antihypertensive medications, including a diuretic. Additional inclusion criteria. March 2007 - November 2009. Subjects divided into Group A n = 181, Group B n = 84 | n = 181 received BAT for full 12 months. All patients implanted with the particular device. | n = 84 received delayed BAT following the first 6 months. | P = 0.005 at six months between the two groups. Overall blood pressure reductio P = < 0.001 | Double-blind randomized trial | Mean reductions in BP has statistical significance however safety end points were not met for this particular device. | Blood pressure medication changes were allowed to be made during trial. |
| Brewster, L M. & Seedat, Y. K., (2013). Why do hypertensive patients of African ancestry respond better to calcium blockers and diuretics than to ACE inhibitors and B-adrenergic blockers? A systematic review. *Biomed Central Medicine, 11*(141), 1-16. | Researchers retrieved 3,763 papers, and included 72 reports that mainly considered the 4 major classes of  antihypertensive drugs, calcium blockers, diuretics, drugs that interfere with the renin-angiotensin system and  β-adrenergic blockers. | Different clinical efficacy of anti-hypertensive drugs in patients of African ancestry. | Patients of African ancestry. | Insufficient. | Using the methodology of the systematic reviews narrative synthesis approach, we sought for published  or unpublished studies that could explain the differential clinical efficacy of antihypertensive drugs in patients of  African ancestry. PUBMED, EMBASE, LILACS, African Index Medicus and the Food and Drug Administration and  European Medicines Agency databases were searched without language restriction from their inception through  June 2012. | Available data are inconclusive regarding why patients of African ancestry display the typical response  to antihypertensive drugs. In lieu of biochemical or pharmacogenomic parameters, self-defined African ancestry  seems the best available predictor of individual responses to antihypertensive drugs. | Large amount of data to read over. |
| Cevik, C. & Iseri, S. O., (2013). The effect of acupuncture on high blood pressure of patients using antihypertensive drugs. *Acupuncture & Electro-Therapeutics Research, 33*, 1-15. | Patients with known hypertension being treated by a cardiologist with antihypertensive medications for a minimum of 2 years.  Initially these patients established for acupuncture treatment for back pain or headache.  Did not alter the diet, exercise level or medications of the patients in the study. | Patients enrolled in an accupuncture program for complaints of back ache or headache.  The selected patients also had hypertension and currently under medication therapy for the same.  Nine points were stimulated and showed a reduction in their blood pressure post treatment. | Blood pressures of the patients were taken pre treatment and post treatment.  There was no control group with this study. | Not published | Not stated. | Treating hypertensive patients with nine specific acupuncture points seems to have a lowering effect on blood pressure and reducing unwanted side effects of medication. | Small population size and limited age range.  N=35. Males aged 15-59 & Females aged 43-80 |
| Dimeo, F., Pagonas, N., Seibert, F., Arndt, R., Zidek, W., & Westhaff, T. H., (2012). Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension, 60*, 653-658. | Total of 50 patients enrolled, from hypertension outpatient clinic with resistant htn defined as bp >= 140/90 in spite of minimum use of 3 antihypertensive agents. Specific exclusion criteria included. | n = 26, participated in 8-12 week (3 times weekly) treadmill exercise program with 24 hour blood pressure monitoring | n = 24, did not participate in 8-12 week treadmill exercise program with 24 hour blood pressure monitoring | Exercise significantly decreased systolic and diastolic daytime ambulatory blood pressure P = 0.03 | Parallel group randomized controlled trial | Aerobic exercise leads to a significant reduction of blood pressure in resistant hypertension.  A low responsiveness to antihypertensive drug therapy does not inevitably go along with a low responsiveness to exercise. | Small sample size |
| Esler, M. D., Krum, H., Sobotka, P. A., Schlaich, M. P., Schmeider, R. E., & Bohm, M., (2010). Renal sympathetic denervation in patients with treatment-resistant hypertension (The Simplicity HTN-2 Trial): a randomized controlled trial. *The Lancet, 376*, 1903-1909. | Patients had to be 18 years of age or older.  They could not have a GFR of <45mL/min per 1.73m2, type 1 diabetics, a known secondary cause or significant renovascular abnormalities. 190 patients from 24 different centers. | Patient's would undergo renal denervation. | 106 patients were randomly selected to undergo renal denervation. | P <0.001. | multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of  160 mm Hg or more (≥150 mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive  drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to  maintain previous treatment alone (control group) at 24 participating centres. | At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10mm Hg or more, compared with 18 (25%) of 51 controls. | Small sample size |
| Gangwisch, J. E., Feskanich, D., Malaspina, d., Shen, S., & Forman, J. P., (2013). Sleep duration and risk for hypertension in women: Results from the nurses’ health study. *American Journal of Hypertension, 26*(7), 903-911. | Women who self reported sleep duration and hypertension from Nurses' Health Study.  Data from 1986(82130), 2000(71658), and 2001(84674). | Self-reported sleep patterns. | 4 age categoried; <50; 50-59; 60-69, and >70. | P <0.001. | prospective, multisite cluster randomized pragmatic trial with randomization of 16 | The Adherence and Intensification of Medications program more rapidly lowered SBPs among intervention patients, but usual-care patients achieved equally low SBP levels by 6 months after the intervention period. | The data was self-reported. |
| Grimmsmann, T., & Himmel, W., (2011). Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes. *European Journal of Clinical Pharmacology, 67*, 847-854. | Monitoring the 149,704 patients who received hypertension medication continuously. | To determine if the defined daily doses (DDD) of antihypertensive medications are different than prescribed daily doses (PDD). | The study compared the various antihypertensive drug classes against one another: thiazide diuretics, beta blockers, dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, ACE inhibitors and ARBs. | Not published | Observational study | The average prescribed daily dose:defined daily dose ratio for beta blockers = 0.84.  For ARBs the ratio = 1.88 and for ACE inhibitors the ratio = 2.17. | The study was done at pharmacies.  The data collected relied on prescriptions actually being filled by the patients. |
| Heisler, M., Hofer, T. P., Schmittdiel, J. A., Selby, J. V., Klamerus, M. L., Bosworth, H. B., Bermann, M., & Kerr, E. A., (2012). Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems. *Circulation, 125*, 2863-2872. | Outpatient primary care clinic at 3 urban VA facilities in the Midwest and 2 KP facilities in California. Patients with DM with poor persistent BP control and poor refill adherence or insufficient medication intensification were included. | n = 1797 Care received by team of pharmacists whom reviewed charts prior to contact, and made changes based on specific protocol criteria previously agreed upon. Monitoring took place as described in control. | n = 2303 Received standard care from PCP for medication adherence and adjustment based on home ambulatory and office monitoring of BP. Monitoring took place 6 months prior to initiation of 14 month interventions through 6 months post interventions. | SBPs at end of quarter 1 dropped significantly compared to control P <0.001 | Prospective multisite cluster randomized pragmatic trial | SBP targets were reached quicker in intervention group but were the same by end of study. | Numerous pharmacists involved making standardization difficult despite steps being taken to do so. |
| Hermida, R. C., Ayala, D. E., Mojon, A., & Fernandes, J. R., (2011). Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. *Journal of American Society of Nephrology, 22*, 1-9. | N=661.  Males and females over the age of 18.  Did include patients with CKD.  Excluded patients who were night shift workers, pregnant and major CVD disorders. | Patients were randomly selected to take their medications in the morning or at bedtime.  Blood and urine samples were obtained along with serial blood pressure readings for 48 hours. | One group of patients assigned to take their medication in the morning and the other group to take their medication at bedtime. | P<0.001 | Open-label trial | (p<0·0001). | Patients with various diagnosis were excluded from this trial and account for a large percentage of those who are regularly treated for hypertension.  Including: pregnant patients, drug users, ETOH abuse, CVD disorders, AIDS, night shift workers, secondary hypertension, type 1 diabetes and kidney failure. |
| Heshka, J., Ruzicka, M., Hiremath, S., & McCormick, B. B., (2010). Spironolactone for difficult to control hypertension in chronic kidney disease: An analysis of safety and efficacy. *Journal of American Society of Hypertension, 4*(6), 295-301. | n = 88 Renal Hypertension Clinic at the Ottawa Hospital reviewed all clinic charts of patients from September 2005 - July 2009.  SBP >= 130/80 despite two antihypertensive agents with or without CKD. 90% on renin-angiotensin system blockade and diuretic. | n = 34 low dose spironolactone in CKD | n = 54 low dose spironolactone in absence of CKD | P = 0.006 | Retrospective cohort design | Significant reduction in BP of difficult to control CKD patients with low dose spironolactone. | Small sample size. |
| Krum, H., Barman, N., Schlaich, M., Sobotka, P., Esler, M., Mahfoud, F., Bohm, M., & Dunlap, M.,(2011). Catheter-based renal sympathetic denervation for resistant hypertension, durability of blood pressure reduction out to 24 months. *Journal of the American Heart Association, 57*, 911-917. | 153 patients at 19 centers in Australia, Europe, and the United states from 6/2007-5/2010.  Patients were enrolled based on having an elevated office systolic BP  ( 160 mm Hg) despite taking  3 antihypertensive drug classes, 1 of  which was a diuretic, at target or maximal tolerated dose. Patients  were excluded if they had an estimated glomerular filtration rate  (eGFR) of  45 mL/min per 1.73 m2, type 1 diabetes mellitus or a  known secondary cause of hypertension other than sleep apnea or  chronic kidney disease. | Catheter based Renal sympathetic denervation. | No control group. | P=<0.05 | Open-label proof of concept study. | We treated 153 patients in this open-label, proof-of-concept  study. Baseline characteristics of the study subjects including  demographics and background medication are listed in Tables  1 and 2. Mean baseline BP values were 176/98 17/  14 mm Hg. Patients were taking an average of 5.1 1.4  antihypertensive drug classes. | There is no control group with which to make comparisons  regarding BP and eGFR responses over time. |
| Lee, J., Aziz, H., Liu, L., Lipkowitz, M., O’Connor, D. T., Richard, E., Brophy, V., Wassel, C. L., Blantz, R., & Bhatnagar, V., (2011). B1-Adrenergic receptor polymorphisms and response to B-blockade in the African-American study of kidney disease and hypertension (AASK). *American Journal of Hypertension, 24*(6), 694-700. | 1094 African American  patients with hypertension nephroscelrosis. | Participants from the African-American Study of Kidney Disease  and Hypertension (AASK) trial were genotyped for ADRB1  polymorphisms: Ser49Gly and Arg389Gly. Cox proportional hazards  models were used to determine the relationship between ADRB1  polymorphisms and time to reach a mean arterial pressure (MAP) of  ≤107 mm Hg in the first year after randomization, adjusted for other  predictors of blood pressure response. | 329 patients were randomized to take metoprolol, 197 men and 132 females. | P=<0.05 | Randomized controlled trial. | Ser49/Gly49 was predictive of blood pressure response to metoprolol  only among more obese African Americans with early hypertensive  nephrosclerosis. In contrast to other studies suggesting increased  short-term responsiveness to β-blockers with Arg389, Arg389  individuals were less responsive in this study analyzing blood  pressure over a 1-year period. | It is unclear how the effect of loss to follow-up or death may bias these results. By design of the original cohort, the results are not readily applicable to other ethnicities or subjects without  hypertensive nephrosclerosis. This study was not sufficiently  powered to detect smaller changes in blood pressure or effects on rare variants such as ADRB1 Gly49Gly. |
| Li, D., Zhou, Y., Yang, Y., Ma, Y., Li, X., Yu, J., Zhao, Y., Zhai, H., & Lao, L., (2014). Acupuncture for essential hypertension: A meta-analysis of randomized sham-controlled clinical trials. *Evidence-Based Complementary and Alternative Medicine,* 1-7. | A possible 2407 articles.  Screening narrowed down to 48 and only 4 were included in the analysis.  N=386 patients with essential hypertension.  223 in acupuncture group; 163 in sham-acupuncture group. | Literature review of four relevant randomized controlled trials of the impact of acupuncture in conjunction with antihypertensive medications to reduce blood pressure. | Comparing acupuncture treatment vs. sham-acupuncture to reduce hypertension. | Not stated | Meta-Analysis of andomized sham-controlled clinical trials | Acupuncture in conjunction with antihypertensives lower blood pressure.  Not supportive of acupuncture alone. | Small sample size of the patients reviewed.  Possibly not all randomized controlled trials relevant to this review were found. |
| Lochner, S., Kirch, W., & Schindler, C., (2012). Managing hypertension among nursing-home residents and community-dwelling elderly in Germany: a comparative pharmacoepidemiological study. *European Journal of Clinical Pharmacology, 68*, 867-875. | Individuals aged 65 years or older with a diagnosis of arterial hypertension. 518 patients. | Investigate the adequacy of hypertension management in hypertensive elderly living in nursing homes compared to those living at home. | 209 patients in long term care facilities and 209 patients living at home. | P=<0.05 | Retrospective, cross-sectional, pharmoepidemiological study. | NH residents showed better  BP control than CD elderly while receiving fewer antihypertensive  drugs. | Data for the CD setting was self-reported by the  patients. The nonrandomized selection of four NHs, which voluntarily  participated out of 23 available in Dresden,  might introduce a bias toward high-quality NHs. |
| Mortsiefer, A., Meysen, T., Schumacher, M., Abholz, H., Wegscheider, K., & Schmitten, J., (2015). From hypertension control to global cardiovascular risk management: an educational intervention in a cluster-randomised controlled trial. *Biomed Central Family Practice, 16*(65), 1-10. | Patients with known hypertension of 87 practitioners. N=3443. Mean age 63.8 | Practices were assigned wither simple intervention or complex interventions and their guidelines were received by mail.  Patients at those practices were then treated with the same.  Data was collected at baseline and then 6-9 months post interventions. | Complex interventions to reduce cardiovascular risk were compared to simple interventions to reduce risk. | Cardiovascular risk from baseline was p<0.001. | Prospective non-blinded longitudinal cluster-randomized controlled trial.  Practices assigned complex vs. simple interventions randomly.  Data collected at baseline and then again at 6-9 months after the interventions. | Complex intervention did not yield higher effects than simple interventions. | Insufficient interventions, too short of a follow up period or patient noncompliance. |
| Mukhtar, O.,  Jackson, S. H. D., (2012). The hypertension in the very elderly trial - latest data. *British Journal of Clinical Pharmacology, 75*(4), 951-954. | Recruitment centres in 13 countries. A total of 3845 older adults with both systolic and diastolic HTN. | One group would receive a thiazide like diuretic for treatment of HTN. | Randomized into a treatment group to receive indapaide and a placebo (control) group. | P <0.001. | A double-blind placebo-controlled trial | anti-hypertensive therapy with  indapamide ( perindopril) reduces all-cause mortality in  octogenarians. | Having recruited large numbers of patients from Eastern Europe and China, the authors were criticized for not appreciating the increased prevalence of cerebrovascular events in these populations,  when compared with adults from Western Europe –a factor which may exaggerate the potential benefit  arising from active therapy [14]. In addition, it was notable that four centres closed in the first year due to data  quality issues. |
| Muntner, P., Anderson, A., Charleston, J., Chen, Z., Ford, V., Makos, G., O’Connor, A., Perumal, K., Rahman, M., Steigerwalt, S., Teal, V., Townsend, R., Weir, M., & Wright, A. T., (2010). Hypertension awareness, treatment, and control in adults with CKD: Results from the chronic renal insufficiency cohort study. *American Journal of Kidney Diseases, 55*(3), 441-451. | CRIC Study, adults aged 21-74 with a broad spectrum of renal disease severity. June 2003 - March 2007 from 13 sites in 7 centers in the United States n = 3612. | No intervention | No control | The prevalence of HTN in CRI patients is 85.7%, 98.9% of these patients were aware of this diagnosis with 98.3% being treated.  Despite this, 67.1% and 46.1% had htn controlled to <140/90 & <130/80 respectively. | Cross-sectional Analysis | Poor treatment of htn in the renal population despite high awareness rates. Better control noted with younger and non-black patients.  HTN more common with higher BMI, current/former smokers, with DM, CV disease.  Control rates were highest in patients using angiotensin receptor blockers and ACE inhibitors versus other meds such as diuretics, B-blockers, and CCB’s. | Single study visit. |
| Neutel, J., Smith, D., Gradman, A., (2010). Adding nebivolol to ongoing antihypertensive therapy improves blood pressure and response rates in patients with uncontrolled stage I-II hypertension. *Journal of Human Hypertension, 24*, 64-73. | N=669 patients.  Men and wome over the age of 18 who had inadequate control of their hypertensionwith their present regimen of medication. | Assessing the response of patients when adding nebivolol to ongoing medication treatments for blood pressure reduction in stage 1 or 2 hypertension.  Patients were assessed on day 14, 42 and 84 with serial blood pressures and ECG monitoring. | A placebo group was used to compare the addition of a placebo to ntihypertensive therapy.  More than twice the amount of patient effect was noted with the nebivolol as with the placebo. | P<0.001 & P<0.028 | Double-blind, plaebo-controlled, parallel-group study. | Blood pressure reduction was seen in patients who had nebivolol added to their medication regimen.  No effect was noted on the serum glucose levels of patients who took nebivolol. | Small sample size. |
| Pimenta, E., Gaddam, K. K., Oparil, S., Aban, I., Husain, S., Dell’Italia, L. J., & Calhoun, D. A., (2009). Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension results from a randomized trial. *Hypertension, 54*, 475-481. | n = 12 c/ resistant htn defined as BP >140/90 on 3 or more antihypertensive meds at effective doses including a thiazide diuretic for at least 4 weeks prior to enrollment. No meds discontinued prior to evaluation. | High Salt diet for 1 week followed by regular diet for 2 week washout period before crossing over to opposite diet for 1 more week | Low Salt diet for 1 week followed by regular diet for 2 week washout period before crossing over to opposite diet for 1 more week | Statistical significance was reached in reduction of office and ABPM in the low-salt diet. P 0.0008 for SBP, P = 0.0065 for DBP | Randomized crossover study | Excessive dietary sodium contributes to resistance to antihypertensive treatment. | Small sample size. |
| Scheffers, I. J. M., Kroon, A. A., Schmidli, J., Jordan, J., Tordoir, J. J. M., Mohaupt, M. G., Luft, F. C., Haller, H., Menne, J., Engeli, S., Ceral, J., Eckert, S., Erglis, A., Narkiewicz, K., Philipp, T., & Leeuw, P. W., (2010). Novel baroreflex activation therapy in reistant hypertension. *Journal of the American College of Cardiology, 56*(15), 1254-1258. | 45 subjects @ 9 clinical settings, implanted between March ’04 and November ’07.  Ages were > 21, with BP >=160/90 and on three antihypertensive agents including a diuretic. Exclusions included high risk patients with carotid stenosis, valvular disorders, | Rheas device implanted in 45 subjects with n =  26 completed 1 year of device therapy and n = 17 completing 2 years of device therapy. Device activation 1 month following implantation. | No device implantation/use | All reductions in BP were statistically significant except for ASBPM @ 3 months due to a measurement error. | Multicenter prospective, nonrandomized feasibility study. | Rheos provided a significant and meaningful reduction in blood pressure in those that were difficult to manage with medications alone. | High number of patients dropped from study, exclusion criteria limits amount of study participants. Small population size. |
| Slagman, M. C. J., Wanders, F., Hemmelder, M. H., Woittiez, A. J., Janssen, W. M. T., Heerspink, H. J. L., Navis, G., & Laverman, G. D., (2011). Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *British Medical Journal,* 1-10. | n = 52 with non-diabetic nephropathy. four 6 week periods of treatment with blood pressure above 125/75, excluding DM, Renovascular htn, cardiovascular event in previous 6 months, immunosuppressive treatment, NSAID use. | low sodium diet in conjuction with standard medications with and without ACE | regular diet in conjunction with standard medications | P < 0.001 for blood pressure reduction with a low sodium diet. Also significantly larger than the reduction of SBP with an angiotensin receptor blockade. | Multicentre crossover randomised controlled trial | Dietary sodium restriction is more effective in blood pressure reduction than dual blockade. | Small population size. Short term data with no hard end points. Limited generalizability of data due to exclusion criteria. |
| Stranges, S., Dorn, J. M., Cappuccio, F. P., Donahue, R. P., Hovey, K. M., Kandala, N., Miller, M. A., Trevisan, M., (2010). A population-based study of short sleep duration and hypertension: the strongest association may be in pre-menopausal women. *The University of Warwick,* 1-13. | Participants were 3,027 white men (43.5%) and women (56.5%) without prevalent cardiovascular disease (median age: 56 years). | Examined the cross-sectional gender-specific associations of sleep duration with hypertension in a large population-based sample from the Western New York Health Study (1996-2001). | No control group. | p=0.003 | A series of case-control studies were performed. Sleep duration in the past week was ascertained with the Seven-Day Physical Activity Recall questionnaire. | n multivariate analyses, short duration of sleep was associated with a significant increased risk of hypertension compared to sleeping 6-8h per day, only among women (OR=1.61 [ 1.08 to 2.41]). No significant associations were found among men (OR=0.88 [0.59 to 1.32]). In subgroup analyses by menopausal status, the effect was stronger among pre-menopausal women (OR=2.77 [1.23 to 6.25]) as compared to post-menopausal counterparts (OR=1.40 [0.88 to 2.23]). | The population under investigation is an occupational cohort of white-collar workers and limited to whites, which may reduce the generalizability of our findings to other populations. Also, information about sleep duration was self-reported by the participants. |
| Turner, S. T., Schwartz, G. L., Chapman, A. B., Beitelshees, A. L., Gums, J. G., Cooper-DeHoff, R. M., Boerwinkle, E., Johnson, J., & Bailey, K. R., (2010). Plasma renin activity predicts blood pressure responses to B-blocker and thiazide diuretic as monotherapy and add-on therapy for hypertension. *American Journal of Hypertension, 23*(9), 1014-1022. | N=363.  Men and women less than 65 years old. | Patients were randomly assigned hydrochlorothiazide then atenolol or atenolol then hydrochlorothiazide.  Home blood pressure readings wre used to assess the patient response to drug therapy. | Age and race were used to renin profile patients. | P<0.05 | Used objectives and design of PEAR study. | Blood pressure responses are predicted with pretreatment.  Blood pressure declined in both groups with the addition of both medications.  Responses with add-on therapy were greater than monotherapy. | Small sample size. N one older than 65 included in the study.  Blood pressures were taken at home. |
| Vaclavik, J., Sedlak, R., Plachy, M., Navratil, K., Plasek, J., Jarkovsky, J., Vaclavik, T., Husar, R., Kocianova, E., & Taborsky, M., (2011). Addition of spironolactone in patients with resistant arterial hypertension: A randomized, double-blind, placebo-controlled trial. *American Heart Association, 57*, 1069-1075. | BP >140/90 despite 3 antihypertensive drugs including a diuretic were enrolled. N = 117 | n = 59 received spironolactone as add-on to medications. | n = 58 placebo | At 8 weeks ambulatory SBP was lower with statistical significance in intervention group P = 0.024 and not significant for DBP P = 0.358.  Night time SBP was P = 0.011, 0.004, and 0.011, night time DBP was P = 0.079, 0.405, 0.079. | Double-blind, placebo-controlled multicenter trial. | Spironolactone is effective in lowering SBP in resistant arterial HTN. | Small sample size |
| Weber, M. A., Basile, J., Stapff, M., Khan, B., & Zhou, D., (2012). Blood pressure effects of combined B-blocker and angiotensin-converting enzyme inhibitor therapy compared with the individual agents: A placebo-controlled study with nebivolol and lisinopril. *Official Journal of the American Society of Hypertension, 14*(9), 588-592. | Patients with stage 2 diastolic hypertension. N=1162. Ages 18-64. | Patients received nebivolol and lisinopril together to determine if the blood pressure lowering effect is greater than the drugs given in the same doses seperately. | A placebo group was used to compare monotherapy of both drugs with the combination therapy. | Combination decresed diastolic BP more than placebo (p<0.0001). Systolic BP reduction was P<0.0001. | Double-blind, placebo-controlled parallel group trial | Nebivolol adds to the blood pressure reducing effect of Lisinopril in patients with stage 2 hypertension.  The combination therapy was more effective than nebivolol alone or Lisinopril alone.  The combination treatment was also well tolerated by the participants. | No elderly included in the study.  An unexpected finding of a placebo effect on BP.  One third of patients in this study were African American.  Maximum dose of nebivolol was not used. |
| Weber, M. A., Black, H., Bakris, G., Krum, H., Linas, S., Weiss, R., Linseman, J. V., Wiens, B. L., Warren, M. S., & Lindholm, L. H., (2009). A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistent hypertension: a randomized, double-blind, placebo-controlled trial. *The Lancet, 374*, 1423-1431. | 117 sites in North & South America, Europe, New Zealand, Australia. 379 patients with SBP > = 140, receiving at least three BP meds including diuretic. | Treated for 14 weeks with medications n = 81 (darusentan 50mg), n = 81 (100mg), n = 85 (300mg). | n = 132 with placebo | P < 0.0001 for all effects in intervention group. | Randomised, double-blind study | Darusentan allows for further reduction in blood pressure in patients on three or more antihypertensives.  Greater SBP decrease at higher dose, but not significant DBP difference in the varied doses. | Exclusion critera such as CHF, poorly controlled DM. |
| Welsh, T., Gladman, J.,  Gordon, A. L., (2014). The treatment of hypertension in care home residents: A systematic review of observational studies. *Journal of American Medical Directors Association, 15*, 8-16. | 6170 records were identified through database searches.  These were screened and 16 articles met eligibility requirements to be included in the quantitative synthesis. | To describe the prevalence of hypertension in care home residents, its treatment, change in treatment over time, and the achievement of blood pressure (BP) control. | No control group. | The prevalence of hypertension in study populations was greater in more recent studies  (P ¼ .004). ACEi/ARBs (P ¼ .001) and b-blockers (P ¼ .04) were prescribed more frequently in recent  studies, whereas use of calcium-channel blockers and diuretics remained unchanged over time. The  number of antihypertensives prescribed per patient was higher (correlation 0.332, P ¼ .009), whereas  fewer patients achieved target BP (correlation  0.671, P ¼ .099) in more recent studies. | The PubMed, Cochrane, Embase, and PsychINFO databases were searched for observational | Hypertension is common in care home residents and is commonly treated with antihypertensive  drugs, which were prescribed more frequently in more recent studies but with no better BP  control. These studies indicate a tendency toward increasing polypharmacy over time, with associated  risk of adverse events, without demonstrable benefit in terms of BP control. | Only a small number of articles (0.003%) qualified for the analysis. |
| Weltermann, B., Viehmann, A., & Kersting, C., (2015). Hypertension management in primary care: Study protocol for a cluster randomized controlled trial. *Institute for General Medicine, 16*(105), 1-6. | The study is conducted in the practice network of 180 primary care academic teaching practices of the University  Duisburg-Essen, Germany. 24 practices volunteered for participation  and fulfilled the inclusion criteria. A total of 169patients wer e enrolled at baseline; of these, 101 (59.8%)  were associated with the intervention arm. | The program aims at changing physician awareness and practice design. Various practice tools are provided. | 101 patients in the intervention arm, 58 in the control group. | Outcomes not available/printed. | Cluster randomized trial with primary care practices as the unit of randomization. | Not published. | Not published. |
| Williams, B., MacDonald, T. M., Morant, S., Webb, D. J., Sever, P., McInnes, G., Ford, I., Cruickshank, J. K., Caulfield, M. J., Salsbury, J., Mackenzie, I., Padmanabhan, S., & Brown, M. J., (2015). Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2):a randomised, double-blind crossover trial. *The Lancet, 386*, 2059-2068. | Patients 18-79 years old. N=335. | Each patient trialed 12 weeks of ironolactone, bisoprostol, doxazosin and a placebo to determine the effects on their blood pressure. | 285 patients took spirinolactone. 282 took doxazosin. 285 took bisoprostol and 274 took the placebo.  Only 230 patients completed all of the four treatment cycles. | Spirinolactone was superior to the placebo. P<0.001 | English language articles involving adults and humans published from 1990 onward. Meta-analysis. | Spironolactone was the most effective out of the add on drugs for treating resistant hypertension and supports the hypothesis of sodium retention related to the condition. | Low number in the sample size. |
| Wright, J. T., Williamson, J. D., Whelton, P. K., Snyder, J. K., Sink, J. M., Rocco, M. V., Reboussin, D. M., Rahman, M., Oparil, S., Lewis, C. E., Kimmel, P. L., Johnson, K. C., Goff, D. C., Fine, L. J., Cutler, W. C., Cheung, A. K., & Ambrosius, W. T., (2015). A randomized trial of intensive versus standard blood-pressure control. *The New England Journal of Medicine, 373*(22), 2103-2116. | 102 clinical sites in US and Puerto Rico. 50 years or older, SBP of 130-180. Total of 9361 participants enrolled November 2010 - March 2013. | Intensive blood pressure management Treatment of n = 4678. Treatment similar to ACCORD trial | Standard blood pressure management treatment of n = 4683 | Cardiac events in intensive control group with numerous meds was statistically lower than standard management P < 0.001. Medications means were 3 for intensive and 1.9 for standard. | Randomized, controlled, open-label trial | BP in intensive group was reduced rapidly with a decreased amount of Cardiovascular events, stroke, and death but required more medications to do so. | Length of study with large amount of participants and keeping treatment streamlined. |
| Wong, M. C. S., (2010). Comparing the cumulative incidences of add-on therapy among the major antihypertensive classes in 2531 asian patients: a cohort study. *Journal of Clinical Pharmacy and Therapeutics, 35*, 201-205. | Patients who were prescribed an antihypertensive medication for the first time in two primary care offices. N=2531.  Mean age 61.  Groups divided as young (<65) and old (>65). | Patients who had never been on antihypertensives were included. | Patients were compared according to age, race, comorbidities as well as drug class.  Medication classes included: thiazide diuretics, beta blockers, calcium chanel blockers and ACE inhibitors. | P<0.05 | Cohort study | There is a wide range of the incidence of add on therapies when comparing drug classes. | Only two centers were used in Hong Kong. |