HYPERTENSION TREATMENT: AN OVERVIEW OF PHARMACOLOGICAL, NUTRITIONAL AND EMERGING INTERVENTIONAL THERAPIES

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Abstract

Hypertension is the leading risk factor for cardiovascular disease and is commonly associated with the development of complications like myocardial infarction, stroke, and heart failure. This disease is often referred to as the “silent killer” because it tends to go undetected until only after an individual has started to present symptoms associated with heart disease and irreversible damage to the heart and vessels that has occurred. Hypertension is clinically defined as systolic over 130 mmHg and diastolic over 80 mmHg, and it is diagnosed after two or more high blood pressure readings on separate occasions. Despite its easy diagnosis, the incidence of hypertension and its associated cardiac complications is still high and increasing among the American population. Moreover, hypertension remains uncontrolled in nearly half of the patient population, even with the addition of traditional pharmacological and lifestyle interventions.

This literature review will provide an overview of hypertension etiology, as well as outline the leading preventative and treatment modalities offered in the clinic today. It will primarily focus on: (1) Medications like ACE inhibitors, beta-blockers, calcium channel blockers, diuretics and angiotensin receptor blockers; (2) Nutrition therapies like the DASH diet; and (3) emerging non-pharmacological therapies like renal denervation or baroreceptor stimulation. Finally, each treatment modality will be compared and discussed, as well as detailing any known interaction of overlapping therapies.

I. INTRODUCTION

Hypertension, also known as high blood pressure, is a multifactorial chronic condition that is the leading cause of cardiovascular disease. It is present in almost half of the American population, and it is often referred to as the "silent killer" due to its late diagnosis and the irreversible health consequences it leads to prior to its detection. While its diagnosis is simple, hypertension is often detected at a stage where the condition has already begun to produce symptoms associated with cardiovascular disease. The reason for this is because hypertension is often asymptomatic throughout its initial stages and goes undetected. As a result, when an individual begins exhibiting symptoms related to heart disease, anti-hypertensive treatment is likely required to lower blood pressure and irreversible changes to the patient's vasculature and cardiovascular system have already occurred.

Since hypertension is a condition that can be caused by a variety of factors, the modification of negative lifestyle habits related to diet, physical activity and substance abuse can heavily contribute to the prevention of hypertension. It is also important to mention that the proper diagnosis and management of hypertension can significantly contribute to the lowering of blood pressure and delay in worsening of the condition. Upon diagnosis, the treatment of hypertension involves the implementation of lifestyle and dietary changes, pharmacological treatment or a combination of the two with the purpose of decreasing blood pressure. Despite its diagnosis, it is also possible for hypertension to be uncontrolled due to the lack of adherence to a treatment plan or accessibility to blood pressure measurements or medications. Therefore, it is important to consider and analyze other forms of therapy like the DASH diet, vegetarianism or emerging therapies like renal denervation that could be alternate forms of treatment and be more suitable to the patient's needs.

Overall, the objective of this review is to provide information on the various methods used for prevention, treatment and management of hypertension. To do this, treatment options involving the use of ACE inhibitors, Beta-blockers, Calcium Channel Blockers, Diuretics, Angiotensin Receptors Blockers, the DASH diet, vegetarianism and renal denervation will be analyzed. Furthermore, the end result of this paper is to create an educational guide that provides information and raises awareness on a serious condition that can lead to severe health effects and that if not properly diagnosed, controlled or treated, can become fatal. To do this, pharmacological, nutritional and emerging treatment therapies will be discussed and a brief summary on their efficacy will be provided.

II. BACKGROUND

Hypertension is the leading cause of cardiovascular disease and the clinical term used to describe high blood pressure (defined as ≥130 mmHg systolic and/or ≥80 mmHg diastolic). It is a multifactorial chronic disease that begins with mild to no symptoms and that can escalate to the development of severe complications that can be fatal if the condition is uncontrolled, undiagnosed or inadequately managed. These consequences include cardiac events like myocardial infarction and stroke and the development of heart failure and kidney disease. The development of hypertension typically occurs due to the presence and combination of several risk factors that include genetics, lifestyle and social determinants. More specifically, modifiable risk factors like obesity, an unhealthy diet that is high in sodium and low in potassium, sedentarism and substance abuse can increase the predisposition of an individual of developing high blood pressure.[1] Therefore, if these factors are adequately identified and modified, the onset of hypertension can be prevented or delayed, and if the condition is already present, modifying these factors can aid in the control and reduction of increased blood pressure.

According to the American Heart Association (AHA) there are five blood pressure ranges. These ranges are: normal (systolic <120 mmHg and diastolic <80 mmHg), elevated (systolic 120 - 129 mmHg and diastolic <80 mmHg), hypertension stage 1 (systolic 130 - 139 mmHg or diastolic 80-89 mmHg), hypertension stage 2 (systolic >140 mmHg or diastolic > 90 mmHg) and hypertensive crisis (systolic >180 mmHg and/or diastolic >120 mmHg).[1] Based on these categories and an individual's blood pressure measurements, it is possible to identify their risk of becoming hypertensive and determine the proper course of treatment. With these readings, it is also possible to categorize these individuals into a blood pressure range that allows the physician to either begin treatment or recommend the implementation of lifestyle changes that will aid in preventing future increased measurements.

In terms of diagnosis, high blood pressure is commonly diagnosed after two or more increased blood pressure readings on two different occasions. Upon detection, the physician will further evaluate the individual's past medical and family history, the presence of risk factors and rule out the possibility of white coat hypertension, which is an increased blood pressure reading in a medical setting but not on an everyday basis.[2] Once the patient has been evaluated, the physician will determine a diagnosis and based on their status, they will intervene pharmacologically or through lifestyle changes.

Despite its simple diagnosis, the incidence of hypertension and its related consequences is high among the American population and often uncontrolled. Due to its increased occurrence, the clinical definition of hypertension was recently redefined, resulting in new blood pressure ranges. The AHA's new hypertension guidelines eliminated the prehypertension stage which was previously defined as systolic 120 - 139 mmHg and diastolic 80 - 90 mmHg, and redefined stage 1 hypertension to systolic >130 and diastolic >80 mmHg.[2] This was done to identify a greater amount of hypertensive individuals and achieve a better diagnosis, control and treatment of the condition. Furthermore, the redefinition of hypertension increased the likelihood of an early diagnosis, better management and lowering of blood pressure and a decreased risk of the disease exacerbating due to the lack of treatment or late detection.

Due to its significant role in the development of cardiovascular disease, it is necessary to briefly acknowledge and discuss the methods available to prevent and manage hypertension. Depending on its causes, hypertension can be classified as primary or secondary. The cause of primary hypertension is unknown but it typically results due to an unhealthy diet, lack of physical activity and environmental factors like obesity, substance abuse and increased sodium intake whereas secondary hypertension is caused by an identifiable and treatable condition like renovascular disease and primary aldosteronism.[1] Based on these classifications, it is then possible to determine a set of preventative strategies that can contribute to decreasing the risk of developing hypertension and if already present, decrease the risk of complications.

While there are several risk factors like age, gender and genetics that are nonmodifiable, the modification of risk factors like obesity, diet, physical activity and lifestyle can be considered preventative. As a result, the implementation of targeted and population-based strategies for the prevention and control of hypertension have been proposed. The targeted approach is already used in health care for management of hypertension and consists of reducing increased blood pressure in patients who are at a higher range or stage of hypertension whereas the population based approach is a public health attempt to reduce blood pressure in the entire population using strategies that are known to decrease increased pressure and the risk for cardiovascular disease.[1] Both of these approaches have been proven effective at preventing and controlling hypertension and tend to apply the same types of lifestyle and dietary interventions.

This review primarily focuses on the different types of therapies used for the control and management of hypertension which include pharmacological, nutrition and surgical therapies. For further information on preventative methods refer to the following reviews: "Prevention and Control of Hypertension: JACC Health Promotion Series"[1] and "The role of diet for prevention and management of hypertension."[3] The first review discusses preventative strategies, the diverse risk factors involved in the development of hypertension, how modifications to these can prevent its onset and the different barriers that influence the control of hypertension. Finally, the second review discusses the role of different types of dietary interventions in the management of hypertension and details on how each type of diet can contribute to the prevention of this disease.

III. PHARMACOLOGICAL THERAPY

While there is no end-all treatment or cure for hypertension, there are several pharmacological agents that manage the progression and severity of hypertension. Depending on their mechanism of action, their target and their side effects, anti-hypertensive pharmaceuticals can be classified as follows: ACE Inhibitors, Beta-Blockers, Calcium Channel Blockers, Diuretics and Angiotensin Receptor Blockers. The use of these drugs depends on the patient's clinical manifestations, their reaction towards the drug and the potential contra-indications of the medication due to underlying conditions. In addition, these drugs can be used as a single or combination therapy in which the patient's treatment consists of receiving one class of drug or a combination of two or three classes to achieve better control of the blood pressure in targeting <130mmHg systolic and/or <80mmHg Diastolic.

The benefits of reducing high blood pressure are well documented and correlated to a decreased risk of both morbidity and mortality attributed to cardiovascular disease. Several studies have demonstrated that a 10 mmHg decrease in systolic and/or diastolic blood pressure is enough to significantly reduce mortality and the likelihood of suffering from major cardiac events like stroke, myocardial infarction and heart failure.[4] This emphasizes the advantages and need of attempting to adequately manage and control increased blood pressure and achieving a blood pressure reading of 130/80 mmHg. To do this, the use of pharmacological agents as a first line of treatment is commonly implemented and individualized to the meet the patient's needs and increase the tolerability and adherence to the prescribed medication.

The variations in pharmacological administration of these drugs depends on the complexity of the patient's disease, the severity of their symptoms and the underlying mechanism that led to its development. Other aspects that are commonly considered while prescribing these medications rely on the potential side effects of each class of drug, their tolerability, contraindications, the drug's bioavailability and their site of action.[5] Therefore, understanding both the pharmacological and health implications of each class of drug can aid in an adequate prescription that is individualized to the patient's needs. Lastly, it is also important to evaluate and understand the efficacy of each class of drug to adequately manage the patient's condition, reduce the risk of side effects, and increase the likelihood of drug adherence.

Angiotensin Converting Enzyme Inhibitors

Since the first approval in the United States in the 1980's, angiotensin converting enzyme inhibitors (ACEIs) have been considered a first-line therapy for the treatment of hypertension and cardiovascular disease due to their primary effect on the reduction of arterial stiffness.[5] The mechanism of action of this drug consists of targeting the renin-angiotensin-aldosterone system (RAAS) by blocking the conversion of angiotensin I into angiotensin II through angiotensin converting enzyme (ACE). This inhibits the effects of angiotensin II type 1 (AT1) and angiotensin II type 2 (AT2) receptors, which are involved in vasoconstriction, sodium and water retention and sympathetic stimulation.[6] The inhibition of these receptors leads to an increase in the vasodilation of blood vessels and subsequently, the reduction of blood pressure. Since angiotensin II is a compound responsible for the vasoconstriction of vessels, inhibiting its production through the use of ACEIs will lead to the reduction of stiffened arteries and hypertrophy of the left ventricle and improve endothelial function and the remodeling of vessels.[5] Additionally, the location of ACE in several tissues like the lungs, capillaries, arteries, venules and kidneys can aid in the modulation of the concentration of angiotensin II in circulation. Therefore, independent from blood pressure changes, the use of ACEIs can further contribute to the improvements observed in renal and arterial function, vessel remodeling and stiffness and cardiac hypertrophy.

In general, ACEIs are very well tolerated and adhered to by patients. However, the increased levels of circulating bradykinin caused by the inhibition of ACE can cause side effects that involve the development of a dry, irritating cough and angioedema.[5] Although these effects are not commonly observed, their manifestation may cause patients discomfort and lead them to withdraw from the medication. As a result, the use of Angiotensin Receptor Blockers (ARBs), a class of drug that will be further discussed in this review, are recommended to patients who experience these negative effects and are proven to be safe and effective and better tolerated and adhered to by patients.[6] Additionally, ACEIs should not be prescribed during pregnancy or to patients who are suffering from hyperkalemia, angioneurotic edema and bilateral renal artery stenosis.

Angiotensin Receptor Blockers

Angiotensin Receptor Blockers (ARBs) are a class of anti-hypertensive drug that have a similar mechanism of action when compared to ACEIs and were developed in an attempt to solve and prevent the side effects that ACEIs produce. Overall, ARBs are commonly chosen as a first choice of treatment for hypertension due to their high tolerability and adherence to by patients and their efficacy at preventing cardiovascular events like heart failure and stroke.[4] Their mechanism of action consists of targeting the blockage of angiotensin II AT1 receptor which is found in high concentrations in smooth muscle and cardiac and renal tissues. The activation of AT1 receptors by angiotensin II leads to cell growth, proliferation and contraction of arteries. To downregulate this, ARBs bind to these receptors in tissues where these are prominent leading to vasodilation, a decrease in total peripheral resistance and ultimately, lower blood pressure.[5] The purpose of targeting angiotensin II receptors rather than its production is to prevent the increased concentration of bradykinin and the upregulation and attenuation of blood pressure lowering effects produced by ACEIs.

When compared to ACEIs, the function and effects of ARBs are not significantly different. Similar to ACEIs, this class of drug has the ability to protect target organs, prevent cardiac hypertrophy and improve endothelial function, arterial stiffening and remodeling and are potent vasodilating anti-hypertensive drugs.[5] The only difference between these two is that ARBs have a decreased risk of side effects and tend to be prescribed in cases where ACEIs are not well tolerated.[6] A common type of ARB used to manage hypertension is olmesartan, which is a long - lasting medication that is more effective at lowering and maintaining blood pressure for a period of 24 hours contributing to a better control of increased blood pressure.[4] Similar to ACEIs, ARBs should not be prescribed during pregnancy and to patients suffering from hyperkalemia and bilateral renal artery stenosis. Overall, angiotensin receptor blockers have also been proven to be a safe and tolerable anti-hypertensive medication that are protective against heart failure and stroke, reduce the risk of proteinuria, and have a lower risk of being discontinued by patients due to their decreased risk of side effects that can include renal dysfunction, hyperkalemia and hypotension.[4]

Beta-Adrenergic Receptor Blockers

Beta-Adrenergic Receptor Blockers, often referred to as "Beta-Blockers", are a common and effective type of medication used for the treatment of cardiovascular diseases like heart failure, coronary artery disease and atrial fibrillation and are considered a second line of therapy for the treatment of hypertension. While this class of drugs are used as the first choice of treatment for several heart diseases, evidence suggest that beta-blockers are not as effective at decreasing mortality, cardiovascular events or stroke when treating essential hypertension.[7] As a result, after further evaluation of beta-blockers, these were removed from being a first line therapy for hypertension. This is because of their pseudo-antihypertensive and heart rate reducing effects that cause a decreased peripheral blood pressure reading while central blood pressure in the aorta remains increased.[8] Furthermore, beta-blockers can lead to a lower heart rate which is often correlated with increased mortality in hypertensive patients. Therefore, this class of drugs has been proven to be more effective at treating patients who are suffering from cardiac complications along with increased blood pressure.

Depending on their cardiac selectivity, agonist activity and vasodilating capacity, the pharmacological properties and mechanisms of action of beta-blockers in reducing increased blood pressure will vary. One of the primary mechanisms of these drugs is through the reduction in cardiac output in the presence of bradycardia. This will increase total peripheral resistance due to the activation of the baroreflex system but will be mitigated by the resetting of baroreceptors. Additionally, due to the reduction of sympathetic activity, vasomotor tone and the release of renin and norepinephrine release will decrease. Based on the characteristics of individual beta-blockers, these can be classified as non-vasodilating with or without B1-seletivity or vasodilating beta-blockers. Compared to each other, vasodilating beta-blockers are associated with a reduction in heart rate, cardiac output, total peripheral resistance and arterial stiffness while non-vasodilating beta-blockers minimally reduce target organ damage, aortic stiffness and central blood pressure.[5] Therefore, non-vasodilating beta-blockers appear to be less effective at lowering blood pressure and its damaging effects.

When it comes to contraindications, beta-blockers should not be prescribed to patients suffering from asthma, unstable heart failure caused by systolic dysfunction, atrioventricular block or sick sinus syndrome and have been proven to potentially contribute to worsening glucose tolerance, increase the risk of diabetes and mask hypoglycemia.[5] Side effects commonly associated to these pharmacological agents typically include vivid dreams, insomnia, hallucination, depression and impotence.[5]

Calcium Channel Blockers

Calcium Channel Blockers (CCBs) are a class of pharmacological agent that have been proven to be effective at treating hypertension in a safe and tolerable manner and that have the ability to lower blood pressure and reduce the likelihood of developing cardiac and renal complications. The primary mechanism of action of this drug consists of blocking L-type voltage dependent transmembrane calcium channels to prevent the movement of calcium through these and decrease the heart's excitability. According to their selectivity to cardiac or vascular L-type voltage channels, CCBs can be classified into the following categories: dihydropyridinic, phenilalchilaminic and benzothiazepinic.

Based on the evidence available regarding these agents, dihydropyridinic CCBs are recommended as a first line of therapy for the control and management of hypertension as well as for their use in combination therapies often involving agents that target the renin-angiotensin system.[9] More specifically, the role of dihydropyridine calcium channel blockers is to prevent the depolarization of vascular smooth muscle cells and cardiac myocytes that are highly dependent on the influx of calcium. Depending on their selectivity, these will provide blood pressure lowering effects through the decrease in repeated depolarization of L-type channels and the prolongation of the inactive state of these channels.

Calcium channel blockers are a type of medication that act as vasodilators of small resistance arteries leading to an increase in coronary blood flow and oxygen supply to the heart and decrease conduction in the atrioventricular node.[5] While CCBs are one of the primary drugs used to control and manage hypertension due to their safety and good tolerability, these can cause a variety of side effects that depend on the dose prescribed. Due to their effect on hemodynamic properties, when administered at high doses, dihydropyridine agents can cause ankle edema, headache, flushing and tachycardia.[9] On the contrary, non-dihydropyridine CCBs can lead to severe bradycardia and impairment of atrioventricular conduction and contractility and should not be prescribed to patients who experience these clinical manifestations, suffer from heart failure or are being administered beta-blockers.[5] However, the occurrence of these effects are not common, and CCBs are considered to be well-tolerated drugs that are effective in lowering blood pressure to target levels in a diverse group of patients including those who are at high risk of complications.

Diuretics

Diuretics are a diverse type of medication commonly used as a primary option of treatment for the control and management of hypertension. The general mechanism of action of diuretics consists of blocking the reabsorption of sodium at the renal tubules leading to an increase in diuresis and natriuresis. Depending on their site of action within the renal tubules, diuretics can be broken down into several therapeutic classes from which loop, thiazide and potassium sparing diuretics will be further discussed. Overall, diuretics have been proven to be as effective at reducing the development of cardiovascular events and stroke in hypertensive patients as other classes of anti-hypertensive medications and play an important role in the treatment of this disease.[10]

Loop diuretics act in the nephron at the ascending loop of Henle and inhibit the reabsorption of sodium and potassium by binding to the transport protein Na/K/2Cl. This leads to an increased delivery of sodium to the distal tubule which promotes the exchange of sodium for potassium and decreases the osmotic driving force of the kidney.[10] The blood pressure lowering effect of loop diuretics consists of decreasing plasma volume, venous return and cardiac output. This occurs in response to an increase in the excretion of sodium which can also stimulate the sympathetic nervous system and the RAAS system.[5]

Thiazide diuretics exert their action in the nephron at the early convoluted distal tubule where they inhibit the reabsorption of sodium and chloride. This occurs by blocking the NaCl cotransporter which increases the delivery of sodium to collecting ducts and promotes the exchange of sodium and potassium.[10] Similar to loop diuretics, the blood pressure lowering effects of thiazide diuretics is through a reduction of plasma volume, venous return and cardiac output. When compared to loop diuretics, thiazide diuretics have a decreased natriuretic effect due their distal action at the convoluted tubule. This indicates that the reabsorption of sodium by these occurs at a lesser extent and therefore have a more short-term effect in the decrease of plasma volume.[5]

In terms of side effects and contraindications, these tend to be dose-dependent and share similar characteristics among subtypes. The side effects of loop diuretics include the following:

hyponatremia, hypokalemia, metabolic alkalosis, hypovolemia, hypotension, hyperuricemia, hypocalcemia, hypomagnesemia, hyper-glycemia, hyperlipidemia, urinary urgency, and impotence.[5] Similarly, thiazide diuretics can lead to the development of these effects with the exception of hypocalcemia which is substituted by hypercalcemia, and both loop and thiazide diuretics are contraindicated in patients with gout. Therefore, it is important to consider the mechanism of action and the potential side effects and contraindications of each subtype of diuretic before they are prescribed.

Another category of diuretics to be considered when treating hypertension include potassium sparing diuretics. This type of diuretic inhibits the reabsorption of sodium at the distal tubule and colleting duct of the nephron and exerts its effect through the inactivation of the epithelium sodium channel (ENaC) and the Na/K pump. When compared to loop and thiazide subtypes, potassium sparing diuretics have a more modest natriuretic effect due to their distal site of action and can lead to hyperkalemia in patients with chronic renal disease, heart failure or diabetes and in those who are taking potassium supplements, ACEIs, ARBs or NSAIDs.[5]

Mineralocorticoid Receptor Antagonists

A significant and more recently developed subtype of potassium sparing diuretics are mineralocorticoid receptor antagonists. These function by preventing the binding of aldosterone to its receptor which decreases the reabsorption of sodium and water into the bloodstream and potentially contributes to lowering increased blood pressure. Common medications found in this category include spironolactone and eplerenone which can be contraindicated in patients with acute or severe renal failure and lead to the development of undesirable side effects due their potential blockage of androgen receptors which can interfere with the function and binding of sex hormones.[11] For example, in the case of spironolactone, this type of medication can lead to reproductive side effects like impotence, decreased libido and bilateral gynecomastia and mastodynia which may be caused by an increased clearance of testosterone.[5]

The primary mechanism of action of mineralocorticoid receptor antagonists consists of blocking the effects of aldosterone which is a mineralocorticoid hormone that plays a role in the maintenance of sodium homeostasis through the regulation of sodium excretion at the level of the distal tubules. Recent evidence shows that this hormone not only functions in regulating sodium levels but also exerts an effect in both heart and blood vessels.[11] When released in excess, aldosterone can lead to endothelial dysfunction as well as vascular, cardiac and renal remodeling which can contribute to the progression of hypertension, heart failure and myocardial infarction. To counteract these disease-causing effects, mineralocorticoid receptor antagonists have been proven effective at managing resistant hypertension and delay the progression of heart failure. Despite these blood pressure lowering effects, mineralocorticoid receptor antagonists have not been proven to have major antihypertensive properties in essential hypertension. However, these have been proven effective in patients with uncontrolled and resistant hypertension and show potential in becoming an additional form of pharmacological therapy for the treatment of this disease.[11]

Due their potential in the treatment of hypertension, the role and safety of mineralocorticoid receptor antagonists like spironolactone and eplerenone is being evaluated and recommendations for their individual use have not been clearly distinguished. Spironolactone was the first mineralocorticoid receptor antagonist to be created and is primarily used for the treatment of hypertension, hyperaldosteronism and peripheral edema. However, this medication can result in negative sexual side effects that lead to the development of menstrual irregularities in women and sexual dysfunction and gynecomastia in males. [12] These sex hormone related effects are attributed to the lack of specificity for mineralocorticoid receptors by spironolactone causing it to bind progesterone and androgen receptors as well. To reduce the occurrence of these effects and increase the tolerability of mineralocorticoid receptor antagonists, eplerenone was developed as an alternative to spironolactone and demonstrates a decreased affinity to sex hormone receptors.[12]

When compared to each other, both of these medications exhibit similar efficacy in the treatment of hypertension and heart failure but slightly differ in their selectivity and production of side effects. Both spironolactone and eplerenone require the evaluation of serum potassium levels and renal function to prevent the development of hyperkalemia, a dangerous side effect commonly experienced with these pharmacological agents. However, due to the increased selectivity of eplerenone to aldosterone receptors, the production of reproductive effects like vaginal bleeding, breast pain and gynecomastia are less likely to occur than when using spironolactone.[12] Furthermore, another important difference between these two pharmacological agents is their potency. While eplerenone is more mineralocorticoid receptor specific than spironolactone, it is less potent and therefore, less likely to cause hyperkalemia or renal dysfunction and complications.[12] On the contrary, spironolactone binds more tightly to mineralocorticoid receptors causing it to have a longer half-life than eplerenone and an increased likelihood and occurrence of sex-hormone associated side effects, hyperkalemia and renal complications.[12] Therefore, the safety, side effects and use of mineralocorticoid receptor antagonists should further be evaluated for the treatment of hypertension and should be considered prior to prescribing these agents.

Overall, evidence shows that mineralocorticoid receptor antagonists are effective in reducing blood pressure while treating several forms of hypertension, primarily resistant hypertension in which the RAAS system plays an important role.[13] Resistant hypertension occurs in patients who are considered to be resistant to anti-hypertensive medications due their inability to return blood pressure to their target reading despite the use of three or more different classes of pharmacological agents. The pathophysiology of patients with this type of hypertension usually involves increased levels of aldosterone and plasma volume suggesting that the use of aldosterone antagonists like spironolactone and eplerenone might be useful for the treatment of resistant hypertension. [13] In combination with other classes of anti-hypertensive drugs, mineralocorticoid receptor antagonists have been proven effective at lowering blood pressure, decreasing damage of target organs and cardiac hypertrophy and preventing arterial stiffness and oxidative stress in patients. However, the effectiveness and safety of this class of pharmacological agent still needs to be determined and further evaluated for patients with essential hypertension.

Pharmacotherapy Summary

Overall, pharmacological agents have been proven to be an effective and safe method of treatment for the control and management of hypertension. Classes of drugs like ACE inhibitors, Angiotensin Receptor Blockers, Calcium Channel Blockers and Diuretics are commonly chosen as first-line of therapy for reducing blood pressure due to their safety, efficacy, good tolerability, decreased risk of side effects and their ability to reduce the development of cardiovascular complications like myocardial infarction, heart failure and stroke. Due to their decreased efficacy in lowering blood pressure when compared to other classes of medications, beta-blockers are now considered a second-line of therapy for hypertension. However, these agents are effective at reducing increased blood pressure in patients with cardiac comorbidities and complications. A newer classification of drugs to be considered when treating hypertension includes mineralocorticoid receptor antagonists like spironolactone and eplerenone. These drugs lower blood pressure in patients with resistant hypertension but require further evaluation due to their sex-hormone related side effects and unknown effects in the treatment of essential hypertension.

Due to the inability to create a drug that effectively and completely targets the mechanism of action of hypertension and solves its clinical manifestations, it is important to understand how each of these drugs functions and the different side effects they produce. To further increase their efficacy and properly target the mechanism behind increased blood pressure in a patient, pharmacological agents can also be used as single or combination therapies and dosage can be adjusted to the meet the patient's needs. Despite their common use and efficacy at reducing increased blood pressure, pharmacological agents have several limitations that might decrease their use and patient adherence. These limitations are primarily related to cost and the occurrence of undesirable side effects such as general malaise, fatigue, orthostatic intolerance, and sexual dysfunction.[5,12] While the availability of generic drugs has lowered costs considerably, the off-target or undesirable side effects have not. Due to these disadvantages, alternative non-pharmacological modalities like dietary interventions, physical activity and lifestyle modifications are available to manage hypertension either separately or in conjunction with pharmacotherapy and should be considered in patient treatment plans.

IV. NUTRITIONAL THERAPY

Despite its severe health effects and easy diagnosis, hypertension tends to go undetected throughout its early stages and is often identified when the patient begins exhibiting clinical manifestations. Due to its late diagnosis and increased risk of cardiac events and complications, patients tend to require an aggressive course of treatment in order to control and lower blood pressure to target levels. As the number of hypertensive patients increases, the need for effective and safe therapeutic strategies to lower blood pressure and prevent its onset is becoming more significant. However, the identification of a therapeutic approach that is effective, safe, tolerable, adherable and properly targets the patient's symptoms has not yet been achieved.

Based on the lack of an effective method of treatment, the use of combined pharmacological and non-pharmacological therapeutic approaches has been proposed to achieve adequate control of advanced stages of hypertension. In cases of early hypertension or increased presence of risk factors like obesity, sedentarism and associated comorbidities, the use of non-pharmacological therapies like lifestyle modifications, physical activity and dietary interventions have been suggested and proven effective at lowering blood pressure and preventing its onset. As a result, strategies like weight loss, exercise and the DASH diet have been proposed as first-line methods of treatment for hypertension.

An important aspect to take into consideration when using these strategies is that an immediate blood pressure lowering effect is not guaranteed upon implementation, and sometimes lifestyle modifications and dietary interventions require the use of additional pharmacological therapies to achieve proper management and control of blood pressure. Despite this, nutritional therapy and lifestyle changes have been proven to be effective at providing long-term management of hypertension, decrease the risk of complications and be preventative in cases where the patient is at risk of developing the disease.

Lifestyle Modifications

Modifiable risk factors like an unhealthy diet, sedentarism, increased body weight, obesity, smoking and alcohol consumption play a significant role in the development of hypertension. If identified early, the modification of these factors can greatly improve and decrease the odds of an individual from suffering of increased blood pressure. Based on the presence of these factors, its complexity and increased risk of complications, the management of hypertension often requires the use of both pharmacological and non-pharmacological therapies. Depending on the hypertensive stage a patient is in, non-pharmacological interventions like lifestyle modifications, weight loss and physical activity can aid in delaying the progression from one hypertensive stage to another and reduce the dosage of pharmacological agents or prevent their use.[14] Therefore, the use of lifestyle interventions can be detrimental at preventing or treating hypertension. However, in order to achieve proper management through the use of a non-pharmacological approach, adherence and compliance to these interventions is key and often a challenge for several patients.

Even though the use of pharmacological agents has been proven to be very effective at lowering blood pressure and preventing cardiac events, complete control of hypertension using pharmacotherapy is not commonly achieved. Therefore, the implementation of lifestyle modifications can be used to return blood pressure to target levels in pre-hypertensive patients and prevent a further increase in patients with stage 1 hypertension. Recent evidence shows that the changes in systolic blood pressure achieved according to different lifestyle changes like behavioral therapy, dietary modifications, physical activity and multiple interventions were of 5.4 mmHg, 3.5 mmHg, 11.4 mmHg and 6.4 mmHg, respectively.[14] These results prove that non-pharmacological interventions can have a direct effect on blood pressure and therefore contribute to its adequate management. Further supporting these results, the American Society of Hypertension recommends attempting 6-12 month lifestyle modifications in patients with stage 1 hypertension and no cardiac complications to control increased blood pressure and hopefully prevent the use of anti-hypertensive medications.[14] These lifestyle changes typically involve the use of various dietary modifications that involve following a plant-based dietary pattern, the DASH diet and a decreased sodium and increased potassium intake. Furthermore, strategies like weight management, physical activity and a decrease in the consumption of alcohol and the use of cigarettes have been proposed to have blood pressure lowering effects.

Weight Loss

Due to the relationship between hypertension and obesity, weight loss has been suggested as a potential strategy for the treatment of high blood pressure in overweight and obese patients. It is also important to recognize that both increased blood pressure and obesity are contributing factors to the increase of cardiovascular risk and therefore adequate management is key to prevent any cardiac complications. The occurrence of hypertension in obese patients can be related to several mechanisms related to insulin and leptin resistance, increased visceral adiposity, dysfunction of perivascular adipose tissue, renal impairment and an increased activation of the renin angiotensin aldosterone system and sympathetic nervous system which are all related to an increased body mass index.[15] As a result, diverse weight loss strategies have been proven to have a positive effect on blood pressure due to a decrease in tissue adiposity and should be encouraged in overweight and obese hypertensive patients.

Weight management strategies include the implementation of lifestyle and dietary modifications, weight loss pharmacological therapy and bariatric surgery. These have been proven to have positive effects on blood pressure and depending on the approach used, these can vary in their blood pressure lowering effect and its durability.[15] Along with lifestyle interventions, weight loss is commonly considered as a first method of treatment for hypertension in overweight and obese patients. Alone or in combination with physical activity, pharmacotherapy and bariatric surgery have been associated with achieving a reduction in blood pressure which can be dependent on the extent of weight loss. To further support and evaluate the impact of weight loss on high blood pressure, a recent clinical trial assessing the effects of changing waist circumference on factors like blood pressure, lipids and glycemia in obese patients was performed. Overall, the study showed that in patients who followed an intensive behavioral weight management program were able to achieve a reduction in waist circumference which led to an improvement in components of the metabolic syndrome where high blood pressure is a contributor.[16]

The mechanism of action behind weight reduction strategies on reducing blood pressure are related to a decrease in adipose tissue and the reversal of the link between obesity and hypertension. Evidence shows that a reduction in visceral adiposity and waist circumference may play a role in improving arterial stiffness and insulin resistance and in reducing vasoconstriction and inflammation.[15] Due to the relationship between perivascular adipose tissue and obesity, weight loss can also be related with improving perivascular dysfunction and reduce vasoconstriction. Additionally, weight loss can also decrease renal adipose tissue and improve natriuresis and sympathetic activation all of which would contribute to lowering blood pressure either independently or in combination.[15] However, despite these beneficial effects, further research is required to evaluate these mechanisms and the durability of a blood pressure improvement.

Plant-Based Diets

While the exact cause of high blood pressure is unknown, this disease is considered to be multifactorial and heavily influenced by lifestyle and nutritional choices that can be detrimental to the health of an individual if chosen poorly. Unhealthy lifestyle and dietary behaviors like an increased consumption of processed foods that are high in fat and low or no intake of fruit and vegetables along with sedentarism have been attributed to an increased risk of developing cardiovascular disease.[17] Due to this association, diverse nutritional interventions like vegetarianism and the DASH diet have been proposed to decrease and potentially reverse the progression of cardiac risk factors that contribute to hypertension and heart disease. Furthermore, recent studies show that incorporating vegetarian or vegan diets to a patient's daily routine can be an effective preventative and therapeutic approach for cardiovascular disease and have been associated with a decrease in mortality and morbidity.[17]

Along with lifestyle modifications like weight loss and exercise, plant-based diets have been associated with a lower blood pressure and are currently being recommended as a potential form of nutritional therapy for the treatment of hypertension. A plant-based or vegetarian dietary pattern consists of reducing or eliminating the consumption of animal products and emphasizes the consumption of fruits, vegetables, whole grains and legumes and depending on the approach may include dairy products. This dietary intervention has been proven to have several beneficial effects in cardiac and even overall health and has been included in the nutrition recommendations outlined by the American Heart Association/American College of Cardiology guidelines.[17] When compared to a traditional American diet or other non-vegetarian dietary patterns, vegetarian or plant-based diets have been proven to cause a greater decrease in systolic and diastolic blood pressure and reduce the risk of developing hypertension in both children and adults. Aside from these effects, plant-based diets impact factors like obesity, insulin resistance and inflammation which are also risk factors for increased blood pressure and are therefore important for reducing the onset of hypertension.[17] However, the mechanism by which plant-based diets exert these beneficial effects and contribute to lowering blood pressure are not entirely known.

Overall, adequately structured vegetarian and vegan diets can provide a healthy lifestyle and adequate nutrition to an individual and at the same time exert beneficial effects in blood pressure that can help hypertensive patients return their blood pressure to target levels and manage their disease. In certain cases, this dietary intervention may require additional supplementation of nutrients that are found in animal products like vitamin B12 and vitamin D to prevent any deficiencies or complications. However, severe side effects caused by this dietary pattern are not common and adherence tends to be good. Based on current evidence and its effect on blood pressure and cardiac risk factors, a plant-based dietary intervention should be promoted as a method of treatment and included in nutritional guidelines used for disease management.

To further support this, results from a recent clinical trial evaluating the effects of a plant-based diet in patients with hypercholesterolemia and hypertension showed that this dietary intervention resulted in significant reductions in systolic and diastolic blood pressure, the use of anti-hypertensive medications and their dosage and in the concentration of serum lipids.[18] The participants in this study were overweight, between 32 and 69 years old and were currently diagnosed with hypertension and elevated LDL levels. Throughout the trial, the patients were instructed to follow a plant-based diet for a period of 4 weeks and their medication dosage was adjusted according to their progress and symptoms. By the end of the trial, the patients exhibited weight loss and a greater improvement in blood pressure than with anti-hypertensive medication indicating the benefits and efficacy of a plant-based diet.[18] According to this trial, the blood pressure lowering effects of this dietary intervention can be attributed to an increased consumption of nitrates, potassium and magnesium along with a decrease in serum lipids through the increased intake of dietary fibers, phytosterol and polyphenols.[18] Based on these findings, it is possible to conclude that the use of nutritional therapies like plant-based diets may be more cost-effective, reduce the use of pharmacotherapy and provide an effective method of treatment for increased blood pressure and cardiovascular risk factors.

Dietary Approaches to Stop Hypertension (DASH) Diet

One of the primary lifestyle modification strategies recommended for the treatment of hypertension is the DASH diet which consists of consuming a diet that is high in fruits and vegetables and low in saturated fats, cholesterol, dairy products, sugar and sodium. Overall, the effects of this dietary intervention have shown to lower increased blood pressure and the risk of developing cardiovascular disease in both adults and adolescents. Recent clinical trials have demonstrated that the DASH diet has been effective at reducing blood pressure in pre-hypertensive and stage 1 hypertensive patients and contributes to a greater reduction of systolic blood pressure when compared to other diets.[19,20] The purpose of the DASH diet was to create a dietary approach that served as an alternative to lower the intake of sodium to help decrease blood pressure without the use of anti-hypertensive medications. On its own, the DASH diet has also been proven to have the same blood pressure lowering effects than that of a single anti-hypertensive medication.[14] Additionally, when combined with physical activity, this type of nutritional therapy can exert both blood pressure lowering effects, potentially reverse the onset of hypertension and delay the use of pharmacotherapy. However, despite these beneficial effects, adherence to this dietary intervention can be an issue for some patients and require the use of pharmacological agents to achieve better blood pressure control.

One of the primary dietary contributors to the development of hypertension is the excess consumption of sodium which can be attributed to its high contents in processed foods. Therefore, it has been proposed that decreasing the intake of sodium can be key in lowering blood pressure. Recent studies have shown that a dietary restriction of sodium and an increased intake of potassium has beneficial effects in the management of hypertension.[14] To achieve this, the DASH diet increases the intake of foods high in potassium, magnesium, calcium and phosphorus through the incorporation of fruits, vegetables and whole grains into the diet and by decreasing the intake of sodium by limiting the consumption of saturated fats, cholesterol and dairy products.

To further support the blood pressure lowering effects of sodium, a recent clinical trial evaluated the influence of the DASH diet in combination with different levels of sodium intake when compared to a control or sodium reduction diet on its own. The participants in the study were hypertensive or pre-hypertensive adult patients whose systolic blood pressure was between 120 and 159 mmHg and their diastolic blood pressure was between 80 and 95 mmHg. The results provided by this study indicate that the combination of reduced sodium intake and the DASH diet caused a decrease in systolic blood pressure across hypertensive patients and lead to a greater reduction in those who started the trial with a higher blood pressure.[19] On the contrary, patients who underwent the normal DASH diet or a low sodium diet alone experienced a lowering blood pressure effect but not to the extent as those following a low sodium DASH diet.[19] This evidence not only indicates that sodium plays a role in the development of hypertension but confirms the efficacy of dietary interventions like the DASH diet in controlling blood pressure. These findings also indicate that combining a reduced sodium intake with a dietary approach like the DASH diet can have major effects in patients who have a higher blood pressure upon implementation. Furthermore, this reinforces the idea that dietary changes and lifestyle modifications can be key in the management and treatment of hypertension and lead to a significant reduction in blood pressure in patients with a higher blood pressure at baseline or whose disease is uncontrolled.

Due to the increased prevalence of hypertension in both adults and adolescents, particularly in those who are overweight and obese, the use of the DASH diet in adolescents as an alternative method of treatment is being explored. Clinical guidelines suggest and emphasize the need of achieving an early diagnosis and intervention at a young age to increase and maintain the likelihood of good cardiovascular health during adulthood.[20] The importance of decreasing blood pressure to target levels in the youth population is due to the link of increased heart and blood vessel damage as well as an increased risk of becoming hypertensive at an earlier stage of adulthood.[20] Therefore, the implementation of lifestyle modifications and nutritional therapy like the DASH diet is being suggested as a first line of treatment of hypertension and has been proven effective at improving dietary habits, blood pressure and cardiovascular health.

A recent clinical trial studying the effects of the DASH diet in adolescents with hypertension showed that this dietary intervention is effective at improving systolic blood pressure, dietary quality and endothelial function in adolescents with elevated blood pressure.[20] The purpose of this study was to assess the effects of the DASH diet after its implementation in adolescents between 11 and 18 years of age and follow up on their effects to evaluate the durability of this approach. In general participants increased their intake of fruits, vegetables and low-fat dairy foods and lowered their intake of saturated fat and sodium and were encouraged to implement physical activity but were not required to. The dietary intervention lasted for 6 months and participants were evaluated after the conclusion of the diet and 18 months later. Overall, the results of the trial showed that upon implementation of the DASH diet, participants who were adherent to this approach were able to achieve an average of a 4.5 mmHg improvement in systolic blood pressure and long-term benefits on endothelial function and vascular health.[20] These results suggest that moderate to high adherence to the DASH diet can lead to improvement and maintenance of decreased blood pressure and vascular health improvement in adolescents and supports the efficacy of this dietary intervention in controlling hypertension without the use of pharmacological agents.

Despite its blood pressure lowering effects, adherence to DASH diet is commonly low and the lack of variability in its food groups can decrease its implementation. In general, the DASH diet attempts to restrict the consumption of sodium and fat and increase the consumption of fruits, vegetables and whole grains. In certain circumstances, this dietary pattern may be hard to achieve by patients and cause them to reject following this approach due to its restrictions. To potentially counteract these restrictive and monotonous effects and increase adherence to this type of dietary intervention, variations of the DASH have been created and evaluated to test for their role in blood pressure management. A recent study tested and compared the effects of a higher fat version of the DASH diet against those of a normal DASH diet pattern. The high fat DASH dietary approach consisted of maintaining the consumption of full fat dairy products and decreasing the consumption of carbohydrates to potentially increase variability in the consumption of macronutrients and preserve the blood pressure lowering effects of the original DASH diet.[21] This diet was then implemented in a group of hypertensive patients and its effects were compared with those of the control diet and the original DASH diet.

Overall, the results of this study showed that the high fat DASH diet lead to a similar reduction of systolic and diastolic blood pressure when compared to those generated by the original diet and indicate that the blood pressure lowering effects of the normal dietary pattern were maintained despite its variations.[21] The modified version of the DASH diet also proved to have an effect on blood lipoproteins resulting in lower concentrations of triglycerides and VLDLs and caused no significant changes in LDL concentrations.[21] These findings support the idea that variations in the original pattern of the DASH diet can potentially increase adherence to this dietary approach due to a reduced list of food restrictions and higher food variability while achieving a comparable reduction in blood pressure. However, limitations to this study include a decreased number of participants and a short trial period. Therefore, the use of variations over the original DASH diet is not widely advised but can be a potential route of treatment to increase adherence and individualize this approach to a wider group of patients.

Summary

Overall, nutritional therapy and lifestyle modifications are currently being recommended as a first-line therapy for patients with pre-hypertension or stage 1 hypertension who are not suffering from additional complications. Depending on the severity and how much control is achieved through these strategies, the use of pharmacological agents may or may not be required throughout treatment. However, the use of dietary interventions like plant-based dietary patterns and the DASH diet along with lifestyle changes like weight loss and physical activity should be closely monitored to guarantee that they are exerting an adequate blood pressure controlling effect and are not causing further complications or exacerbation of the disease. If implemented correctly, lifestyle and dietary modifications can effectively treat and potentially reverse hypertension and provide long-term beneficial health effects.

Based on evidence provided by several clinical trials, the use of nutritional therapy and lifestyle changes should be recommended as a therapeutic approach for the prevention and management of hypertension in clinical settings. However, an important factor to consider when using these therapeutic approaches is the patient’s ability to adhere to the recommendations and the changes required for these therapies to be effective. Due to a potential lack of diet variability, restriction and the high level of commitment involved, patients often tend to fail to adhere to these interventions and opt for another method of treatment that is more achievable for them. Therefore, emerging therapies like renal denervation, baroreflex activation and carotid sinus stimulation are currently in development and may be able to improve patient compliance to hypertension treatment.

V. EMERGING THERAPIES

As the number of hypertensive patients continues to increase, new therapeutic approaches that attempt to lower blood pressure and achieve a long-term control of this disease are emerging. After the clinical definition of hypertension was recently updated and redefined by the American Heart Association to 130/80 mmHg, the prevalence of hypertension in the US increased from 32% to 46%.[22] With this rise in diagnosis, a larger number of patients are requiring the implementation of anti-hypertensive therapies to manage increased blood pressure and prevent the development of cardiac complications. However, despite the availability and efficacy of diverse therapeutic approaches involving the use of pharmacological agents and dietary and lifestyle modifications, a wide number of patients are still unable to achieve proper blood pressure control and therefore require a more complex course of treatment. This is particularly observed in patients with resistant hypertension who despite receiving 3 or more blood pressure medications, they fail to achieve a blood pressure reduction to appropriate target levels. Therefore, alternative methods using device-based therapies that increase patient compliance, or bypass it altogether, may achieve a long-term reduction of blood pressure and minimize the occurrence of undesirable side effects.

Minimally invasive procedures like renal denervation or device-based therapies like baroreflex activation and carotid stimulation are currently under development and are proposing promising effects for the treatment of hypertension.[22] Due to the role of the autonomic nervous system in the development of hypertension, emerging therapies are targeting these mechanisms through the use of neuromodulation strategies to reduce sympathetic activation and a concomitant lowering blood pressure. Detailed below are the current emerging therapies for hypertension treatment and their targeted approach.

Renal Denervation

As the prevalence of hypertension increases, the need to control and reduce blood pressure has led to the development of alternative therapies. While pharmacotherapy is the primary method of treatment for hypertension, adherence by patients to their prescribed medications is not commonly achieved. This is largely influenced by the development of side effects that decrease the drug's tolerability and therefore the patient's compliance to treatment. It is estimated that up to 50% of patients become partially or completely non-adherent to their anti-hypertensive medication within the first year of initiating treatment.[23] Due to the poor compliance observed or the drug-resistant phenotype, device-based therapies like renal denervation are proposed as a potential alternative or complementary method of treatment with a decreased risk of side effects.

Although hypertension is a multifactorial disease, the sympathetic nervous system plays a central role in its pathogenesis and can be easily targeted using either device-based modalities.[23] Where pharmacological treatments function by targeting the nervous system (e.g. adrenergic receptor blockers), targeted denervations can localize treatment to an organ/tissue while maintaining sympathetic innervation elsewhere. Renal denervation is a selective method of treatment that functions by altering the activation of renal sympathetic nerves to suppress renin release, tubular sodium reabsorption and renal vasoconstriction to potentially lower blood pressure while avoiding the development of adverse effects.[23,24]

Due to the proximity of renal nerves to the renal arteries, catheter-based radiofrequency ablation was introduced as a potential method to interrupt renal nerve activity and lower blood pressure in hypertensive patients. The first ablation system developed for renal denervation consisted of a single unipolar electrode on a flexible catheter that functioned by creating multiple lesions through the renal arteries.[23] To test the effects of the Symplicity Flex Ablation Catheter, a series of studies were performed in patients with resistant hypertension. The Symplicity HTN-1 and the Symplicity HTN-2 trials showed the efficacy and safety of this device and patients who underwent renal denervation proved to have a sustained decrease in office blood pressure.[23,24] While the results of these studies were similar, the conditions of each trial differed and lacked a blinded, surgical sham treatment group. In the case of the Symplicity HTN-1 trial, a total of 45 patients underwent catheter based renal denervation whereas in the Symplicity HTN-2 trial 106 patients were randomly assigned to a control or treatment group and were then evaluated.[24]

A follow-up trial, Symplicity HTN-3, was designed to accommodate for the weaknesses of the previous trials by employing a blinded, sham-controlled intervention design. The study consisted of patients presenting with a systolic blood pressure above 160 mmHg and were prescribed at least 3 antihypertensive medications. These patients were then randomly assigned to a renal denervation or sham treatment group. After 6 months, patients who underwent renal denervation experienced a mean decrease in systolic blood pressure of 14.1 mmHg; however, the sham group also displayed a mean decrease of 11.7 mmHg.[23] However, despite the reduction in blood pressure achieved, the results of the study did not detect a significant difference between the renal denervation and the sham group indicating that the efficacy of this treatment was not achieved.[24] As a result, the data generated by the Symplicity HTN-3 trial failed to support the evidence produced by previous trials and the blood pressure lowering efficacy of this device. Post-hoc analysis of the Symplicity HTN-3 trial was performed to reconcile the differences in the findings between the previous Symplicity trials and the current HTN-3. Several analyses indicated that the failure of the trial was likely due to inadequately performing the renal denervation procedure, a medication change of 39% of the patients throughout the trial, and a decrease in the blood pressure of African Americans in the sham group that was not observed in other subgroups of the study.[24] Due to this failure, further study design and device optimization were pursued to correct for these study errors.

In recent years, a second-generation radiofrequency ablation system was developed, The Symplicity Spyral Catheter, which consists of using a flexible 4-electrode array mounted on a catheter to create 4 simultaneous lesions in a helical pattern. In comparison, the previous catheter system was a monopolar, single electrode. To test the efficacy of this system, two trials using this device along with a comprehensive denervation technique involving ablation in the distal main renal artery and arterial branches were developed.[23] Both of these trials included participants with combined systolic and diastolic hypertension and implemented ambulatory blood pressure as a primary endpoint. Patients were also blinded and randomized to a renal denervation or a sham treatment group.

The first study was the HTN-OFF MED trial which consisted of evaluating renal denervation in patients with mild to moderate hypertension (office systolic pressure between 150 mmHg and 180 mmHg and a diastolic pressure greater than 90 mmHg) without the use of medications and an ambulatory pressure between 140 mmHg and 170 mmHg. The 3 months post intervention results revealed a significant decrease in ambulatory blood pressure of approximately 10 mmHg systolic and 5.3 diastolic pressure and no detectable changes in the sham group. [24] Analysis of the results produced by this trial revealed a between-group difference of 5.0/4.4 mmHg [23] indicating a higher blood pressure change by the renal denervated when compared to the sham treatment group. Furthermore, the evidence provided by this study showed a significant decrease in ambulatory blood pressure from baseline to 3 months in renally denervated patients and therefore favored this technique.[23]

The complementary follow-up study, Spyral ON-MED Trial, consisted of enrolling patients with an office systolic pressure between 150 mmHg and 180 mmHg, an office diastolic pressure greater than 90 mmHg and a 24-hour ambulatory systolic pressure between 140 mmHg and 170 mmHg. Aside from meeting blood pressure criteria, patients were also required to be on 1 to 3 anti-hypertensive medications to be enrolled. After randomization, patients in the renal denervation group showed a significant decrease in ambulatory pressure from baseline to 6 months but no changes in the control group.[23] Upon analysis, the results showed a 7.4/4.1 mmHg between-group difference that favored renal denervation.[23] Taken together, the ON-MED and OFF-MED trials carefully isolated the variance of denervation and drug adherence observed in the Symplicity HTN-3 trial, and revealed a significant effect of renal denervation on blood pressure in hypertensive patients. Therefore, the results provided by these trials support the use of renal denervation as a potential treatment for resistant hypertension.

Despite the conflicting results of the Symplicity HTN trials, new techniques for performing renal denervation through catheter-based ablation are continuing to emerge, including the Elipse Sham Device (ENLIGHTEN Trial); Ultrasound DNX and Peregrine catheter. Although the results are promising, the mechanisms mediating the anti-hypertensive effect and the case-based use of this technique remain unclear, and further investigation is required before widespread clinical application.

Baroreflex Activation and Carotid Body Stimulation

Resistant hypertension is largely mediated by sodium overload, arterial stiffness, endothelial dysfunction and high sympathetic activity.[25] With these mechanisms in mind, device-based therapies have been developed and are being proposed as a potential form of treatment for resistant hypertension. Most emerging device-based therapies primarily rely on reducing sympathetic outflow to lower blood pressure and have shown promising results. Similar to renal denervation treatments like baroreflex activation and carotid body stimulation are under investigation to lower sympathetic tone throughout the vasculature and potentially mitigate hypertension.[25] However, evidence on their safety and efficacy is very limited and requires further investigation.

Baroreceptors are stretch-sensitive fibers located in the carotid sinus that are involved in maintaining normal blood pressure levels by participating in negative feedback mechanisms. These receptors are activated upon the stretch of blood vessel walls which triggers a signaling cascade that travels across the nucleus tractus solitarius, the caudal ventrolateral medulla and the rostral ventrolateral medulla. This results in a reduction in sympathetic tone and an increase in parasympathetic activity causing vasodilation and normalization of blood pressure. Based on this mechanism, it is proposed that baroreceptor sensitivity is reset to a higher pressure in hypertensive patients, and can be attributed to direct receptor damage or modification that changes the coupling between receptors and decreased distensibility of the vascular walls.[25] Therefore, it is believed that the amplification of baroreceptor activity can contribute to lowering blood pressure leading to the development of electrical and mechanical device-based therapies that target this mechanism.

The first-generation electrical carotid sinus stimulation device was developed to improve previously developed carotid baroreceptor pacemakers that caused nerve injury and was called the Rheos device.[25] The Rheos device consisted of bilateral electrodes and an implantable pulse generator that are surgically placed around carotid sinuses leading to the activation of baroreceptors. To measure its efficiency, several preclinical and then clinical trial were conducted in resistant hypertension. Evidence from these studies demonstrated a reduction in mean arterial pressure in patients who were stimulated with this device and exhibited a long-term reduction in blood pressure upon follow-up.[25] However, due to its mixed results, poor battery life and invasiveness, this device was not approved by the FDA and its use was discontinued.[25]

To counteract these effects, a second-generation device called Barostim neo was created and is currently being clinically used in Europe. This Barostim neo device consists of a unilateral electrode and an implantable pulse generator that is then inserted onto the arterial wall to stimulate the carotid sinus which allows for a decreased invasiveness and improved battery life. The use of this second-generation device has been proven effective at improving sympathetic vasoconstrictor tone and blood pressure in a wide variety of patients experiencing resistant hypertension including those with renal failure and heart failure with reduced ejection fraction.[25] However, despite these promising results, further studies are needed to confirm these blood pressure lowering effects and to determine the safety and efficacy of this device for the treatment of resistant hypertension.

An alternative to electrical baroreflex activation is mechanical baroreflex amplification. This technique consists of using an endovascular implant to increase circumferential and longitudinal wall strain at the level of carotid baroreceptors in an attempt of activating the baroreceptor reflex and decreasing blood pressure. To test for these effects, the MobiusHD device was developed. Studies evaluating this mechanical device in humans showed a reduction of blood pressure but with the development of adverse effects like hypotension, worsening hypertension, leg claudication and wound infection in several subjects.[25] Therefore, additional trials are required to determine the mechanism of action of this device and evaluate its efficacy, safety and long-term results.

Increased activity of carotid bodies is believed to increase central sympathetic drive and contribute to the development of hypertension by directly increasing sodium retention, renin secretion and arterial resistance. One of the first methods proposed to solve this problem was carotid body resection. This was based on the acute reduction observed in diastolic and systolic blood pressure in asthmatic patients after the resection of carotid bodies.[25] However, due to its invasiveness and failure to show sustained blood pressure reductions, this technique is not entirely proposed for the treatment of hypertension. As a result, catheter-based interventions used for carotid body modulation are being developed and appear to be safe and possess a blood pressure lowering effect.

Overall, the role of baroreceptors is to stabilize blood pressure around a set value by decreasing sympathetic and increasing parasympathetic activity. This mechanism is thought to be altered in hypertensive patients and is therefore targeted by therapies like electrical carotid sinus stimulation, which is believed to decrease blood pressure through afferent baroreceptor activation and provide long-term blood pressure control.[26] To achieve these results, electrical carotid sinus stimulation improves the imbalance between sympathetic and parasympathetic outflow to reduce blood pressure in patients with resistant hypertension. However, due to the variations in the pathophysiology of essential hypertension, this type of device-based therapy may not be effective in some patients.[26]

In general, the function of implantable carotid stimulators consists of producing an electrical field through the stimulation of the carotid sinus to cause the activation of carotid baroreceptors. During their surgical insertion, the position of these electrodes is adjusted to achieve an optimal acute blood pressure reduction. Once the electrodes are placed and fixed, a pacemaker device is connected and adjusted using an external software after the appropriate surgical recovery period. The two generations of carotid sinus stimulation devices include the Rheos device, which was discontinued, and the Barostim Neo device which is currently under review and was recently approved for use in patients who had previously been implanted with the Rheos device and achieved successful blood pressure control.[26]

Evidence from recent uncontrolled clinical trials support the potential of electrical carotid sinus stimulation devices for the treatment of resistant hypertension and suggest beneficial effects of this treatment on cardiac, vascular and renal damage.[26] While electric carotid sinus stimulation has antihypertensive effects, its clinical application can be limited due to its invasiveness. As a result, an alternative method using magnetic stimulation on the carotid sinus (MSCS) was developed to decrease invasiveness and effectively reduce increased blood pressure. The mechanism behind this procedure involves the activation of carotid baroreceptors using magnetic stimulation to convert a magnetic field into induced electrical currents in tissues within its reach leading to an immediate decrease of blood pressure upon stimulation.[27]

To further support this proposed alternative method, a recent clinical trial evaluated the role of magnetic stimulation on blood pressure in pre-hypertensive and hypertensive subjects. The trial included patients between 20 and 70 years of age with a systolic blood pressure higher than 130 mmHg who were randomly assigned to a control or a MSCS group. Participants in the MSCS group received 1 Hz stimulation whereas the control group received sham stimulation. Upon data analysis, the results of the study showed a significant reduction in systolic and diastolic blood pressure, mean arterial pressure and heart rate in patients who underwent MSCS when compared to the control group.[27] These findings suggest the potential of this treatment in reducing blood pressure in pre-hypertensive and hypertensive patients, and if further studied and developed, MSCS can potentially lower blood pressure through a portable or wearable magnetic stimulation device. However, this trial had several limitations related to a small sample size, differences in carotid activation based on age and long-term stimulation and blood pressure reduction are unclear.[27] Therefore, further studies are required in order to completely determine the role of MSCS in reducing blood pressure and its role in the treatment of hypertension.

VI. CONCLUSIONS

Hypertension is a complex multifactorial disease that is characterized by high blood pressure (systolic pressure >130 mmHg and diastolic pressure >80 mmHg) and has an increased risk for cardiac complications like myocardial infarction, stroke and heart failure. Due to its delayed diagnosis, this disease is commonly referred to as the "silent killer" and is detected upon the exhibition of clinical manifestations or the occurrence of a cardiac event. Overall, the development of hypertension is typically influenced by a variety of modifiable risk factors like obesity, sedentarism, increased sodium intake and substance abuse. As a result, following preventive measures such as weight loss, physical activity and dietary and lifestyle modifications can be detrimental to a patient's health and can decrease their risk of becoming hypertensive. Furthermore, as the prevalence of hypertension continues to increase, an early diagnosis of this disease can be key when determining an adequate method of treatment, and in some cases, it can trigger the implementation of behavioral interventions that can reduce blood pressure to target levels and decrease the risk of complications and use of pharmacotherapy.

Depending on its stage and progression, the treatment of hypertension may require a combination of pharmacological and non-pharmacological therapies to achieve proper blood pressure control. Overall, there are five primary classes of anti-hypertensive medications that can be used as a single or combination form of therapy and include: ACE inhibitors, Angiotensin Receptor Blockers, Beta-Blockers, Calcium Channel Blockers and Diuretics. These agents have been proven effective at reducing blood pressure and decreasing the risk of developing cardiac complications in patients with hypertension. Despite their blood pressure lowering effects, adherence to these medications is not commonly achieved due to the production of undesirable side effects. In addition to these agents, mineralocorticoid receptor antagonists are currently being evaluated and have been proven effective in the treatment of resistant hypertension. However, the effects of these agents in essential hypertension still requires further investigation and their use is limited due the production of various sex-hormone related side effects.

Another method of treatment for hypertension that has been proven effective is nutritional therapy. This non-pharmacological method involves the use of lifestyle modifications and dietary interventions like a plant-based diet or the DASH diet to improve risk factors that can trigger the onset of hypertension or exacerbate its progression. Strategies like weight loss, decreased sodium intake and an improved dietary pattern have all been proven to have blood pressure lowering effects in both pre-hypertensive and stage 1 hypertensive patients. Depending on the patient's severity of hypertension, the use of this approach can also prevent or delay the use of pharmacological agents and effectively control blood pressure and improve cardiac health. Furthermore, in cases where hypertension is uncontrolled or more advanced, patients may also benefit from implementing nutritional therapy because of its potential in improving blood pressure management and reducing risk factors like obesity and increased dietary sodium intake which can lead to complications. Similar to pharmacotherapy, this approach is also limited by the lack of patient compliance to these interventions. This is typically caused by the restriction and commitment involved in following a strict dietary pattern, and if neglected or unfollowed, it can lead to a further increase in blood pressure.

Based on the production of undesirable side effects and the lack of adherence to various types of therapeutic approaches, emerging therapies like renal denervation, baroreflex activation and carotid sinus stimulation are currently under development and evaluation for the treatment of hypertension. Due to the major role of the autonomic nervous system in the control of blood pressure, these alternative forms of treatment attempt to lower blood pressure by regulating the interaction between the sympathetic and parasympathetic branches of the nervous system with the production of minor side effects. The use of these interventions also hopes to increase patient compliance and achieve long-term control of blood pressure. To further support this, evidence provided by several studies have demonstrated the effectiveness of these therapies and favor the potential of these in the treatment of hypertension. However, despite these promising results, the safety, efficacy and mechanism of these therapeutic approaches require further investigation before they can be applied in a clinical setting.

While the guidelines for the treatment of hypertension seem to be well established, alternative therapeutic approaches are constantly being investigated with the hope of finding therapies that would solve or improve the limitations of current pharmacological, nutritional and device-based therapies. Due to its complexity, hypertension is a disease that often requires a high level of individualization to adequately target and improve a patient's clinical manifestations. Therefore, pharmacotherapy, dietary interventions and emerging therapies provide physicians with a variety of approaches that can help patients improve their quality of life, decrease their risk of cardiac complications and receive care that is targeted to meet their needs. Despite their beneficial effects on blood pressure and potential in improving cardiovascular health, these methods of treatment fail to cure hypertension and seem to mainly contribute to disease management. Furthermore, these therapies can be used individually or in combination until adequate blood pressure levels below 130/80 mmHg are achieved.

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