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Review Article

Hypertensionand Comorbidities: Exploring Interconnections and Advances in Management

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A B S T R A C T

Hypertension (HTN) is a major worldwide health concern, frequently exacerbated by its close links to chronic illnesses like diabetes and asthma. The complex interactions between hypertension and associated comorbidities are examined in this review, with a focus on common pathophysiological processes such as oxidative stress, systemic inflammation, and dysregulated renin-angiotensin-aldosterone system (RAAS) activation. The risk of cardiovascular and renal problems is greatly increased when these linkages are present, especially in those who have diabetes and asthma. In order to lower morbidity and mortality in hypertensive individuals with diabetes, it is vital to achieve strict blood pressure management, as evidenced by large-scale studies like the HOT and ABCD trials. The management of hypertension is further complicated by inflammatory endotypes linked to asthma, which calls for specialised treatment strategies.Significant progress has been made in personalised medicine with recent developments in the treatment of hypertension, such as the use of mineralocorticoid receptor antagonists, endothelin receptor blockers, and novel chronotherapy. These tactics seek to minimise side effects while optimising blood pressure regulation. However, safety issues and the need for more study to confirm these medicines' long-term effectiveness pose challenges to their application. In order to enhance outcomes and lessen the worldwide burden of disease linked to hypertension, this review emphasises the use of specific medicine in the management of hypertension and its comorbidities and promotes a patient-centric approach.

Keywords: Hypertension, comorbidities, diabetes mellitus, asthma, renin-angiotensin-aldosterone system, systemic inflammation, precision medicine, chronotherapy, cardiovascular risk, personalized treatment.

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INTRODUCTION

The subtle link between Hypertension (HTN) and other health issues like diabetes mellitus (DM) and asthma is a worrying problem that demands our immediate attention. Since its symptoms can be mild or nonexistent, HTN frequently goes undiagnosed. Globally, HTN is the leading cause of cardiovascular illness and early mortality. The development and use of antihypertensive drugs has contributed to a slightly stable and declining worldwide mean blood pressure during the last few decades. One in three adults worldwide suffer from HTN, and approximately four out of five are not receiving adequate treatment, according to a WHO report released in September 2023. Millions of people worldwide suffer with HTN, which is characterised by increased blood pressure and is frequently referred to as the "Silent Killer." [54]Systemic arterial HTN (hereafter referred to as HTN) is characterized by persistently high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of the systolic BP (that is, the pressure that the blood exerts on the arterial walls when the heart contracts) and the diastolic BP (the pressure when the heart relaxes)[1]. HTN is the most common preventable risk factor for Cardiovascular disease (CVD); including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease), Chronic kidney disease (CKD) and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide[1][2]. Healthy and unhealthy blood pressure ranges (Table 1).

Table 1: Understanding Blood Pressure Readings American Heart Association

Blood Pressure Category	Systolic Mm Hg (Upper Number)	And/Or	Diastolic Mm Hg (Lower Number)
Normal	Less Than 120	And	Less Than 80
Elevated	120-129	And	80-89
High Blood Pressure – Stage 1 (Htn)	130-139	And	Less Than 80
High Blood Pressure – Stage 2 (Htn)	140 Or Higher	Or	90 Or Higher
Hypertensive Crisis	Higher Than 180	And/Or	Higher Than 120

Asthma can be defined and simply known as a long-term inflammatory condition of the airways. The recurrent episodes of wheezing, dyspnoea, chest tightness, and/or coughing, which can vary in intensity and duration over time, are linked to chronic inflammation and airway hyperresponsiveness, which is an exaggerated airway-narrowing response to certain triggers like viruses, allergens, and exercise [14].Hundreds of millions of individuals worldwide suffer from asthma and HTN, which coincide more often in adults than would be predicted by chance [3, 4, 5]. Regardless of conventional risk variables, asthmatics had a higher likelihood of having HTN than non-asthmatics in a large population-based investigation [6]. This implies that each person with asthma has a distinct set of risk factors for HTN. One such feature could be decreased lung function (FEV1) and the resulting inflammation. The idea that inflammation in asthma is systemic rather than only restricted to the airways is becoming more widely accepted [7]. HTN risk may also be increased by asthma comorbidities including rhinitis and atopy, which are also linked to low-grade systemic inflammation [7]. Given that long-acting bronchodilators have been linked to death in asthma subgroups, asthma medicines may have side effects of their own [8].

Diabetes mellitus, alsosimply known as diabetes which is a complex metabolic disorder characterized by hyperglycemia, a physiologically abnormal condition represented by continued elevated blood glucose levels. Hyperglycemia results from anomalies in either insulin secretion or insulin action or both and manifests in a chronic and heterogeneous manner as carbohydrate, fat, and protein metabolic dysfunctions [15].HTN is present in more than 50% of patients with DM and contributes significantly to both micro and macrovascular disease in DM[9]. Indeed, the risk for CVD is four-fold higher in patients with both DM and HTN as compared to the normotensive non-diabetic controls [9-11]. To this point, a meta-analysis of 102 prospective studies involving 698,782 individuals found that DM is responsible for approximately a two-fold increased risk for coronary heart disease, stroke and deaths from cardiovascular cause, including heart failure, cardiac arrhythmia, sudden death, hypertensive disease, and aortic aneurysms [12].

INTERCONNECTION BETWEEN HTN AND DIABETES MELLITUS

Inappropriate RAAS activation, oxidative stress from excessive reactive oxygen species (ROS) production, inflammation, impaired insulin-mediated vasodilatation, elevated sympathetic nervous system (SNS) activation, dysfunctional innate and adaptive immune responses, and abnormal renal handling of sodium are some of the pathophysiologic mechanisms that DM and HTN share. [9]. One of the main pathophysiological reasons for both DM and HTN to coexist is obesity and increased visceral adiposity. [9] [16]. Increased synthesis of angiotensinogen (AGT) and angiotensin II (Ang II) in adipose tissue due to chronic low-grade inflammation and oxidative stress causes tissue RAAS activation. Moreover, high blood pressure is caused by AGT overexpression in white adipose tissue. As a result, AGT and Ang II affect blood pressure regulation both locally and systemically. [9][17] [18]. Many of the negative effects of Ang II are caused by activation of the Ang II type 1 receptor (AT1R) (24). In non-adrenal tissues, AT1R activation causes a variety of intracellular processes, such as the generation of reactive oxygen species (ROS), decreased insulin metabolic signalling, and proliferative and inflammatory vascular responses that lead to endothelial dysfunction, insulin resistance, and HTN (24). Therefore, when DM and HTN coexist, an active RAAS is frequently present [9][19].

About 50% of hypertensive patients have systemic insulin resistance, indicating that insulin resistance is a significant factor in the development of both DM and HTN [9]. Two main processes are triggered when insulin binds to its receptor (IR). Increased insulin-mediated glucose transport occurs in insulin-sensitive tissues like skeletal muscle as a result of a metabolic signalling pathway mediated by phosphatidylinositol 3-kinase (PI3K), downstream protein kinase B signalling, and glucose transporter 4 (GLUT-4) translocating to the plasma membrane [9][20]. The balance between these vasoconstrictor and vasodilatory activities favours vasodilation when insulin sensitivity is normal. Deficient insulin metabolic signalling frequently coexists with uncontrolled growth pathway signalling in insulin-resistant conditions [9]. Crucially, insulin reduces sodium excretion via improving sodium reabsorption in the diluting portion of the distal nephron, partly by upregulating the expression of sodium transporters such as the epithelial sodium channel (ENaC) [9][21].

Increased activation of sodium hydrogen exchanger activity in the proximal tubule and effects on ENAC farther out are two possible ways that hyperinsulinemia-mediated sodium retention may contribute to the development of HTN. Although this theory is appealing, in an animal model where IR was knocked out in the renal tubule epithelial cells, the lack of insulin action led to poor natriuretic responses and HTN, most likely as a result of decreased NO generation [9][22]. These conflicting findings necessitate more research to elucidate the physiological function of insulin in renal salt management. Finally, because sodium and uric acid are

typically treated together, excess uric acid can rise in tandem with sodium retention, leading to hyperuricemia, a condition commonly observed in patients with HTN [9][23].

According to the HOT trial, the risk of major cardiovascular events was halved for the 1501 patients with DM at baseline who had stricter blood pressure control (mean blood pressure 140/81) compared to the control group (mean blood pressure 144/85). Individuals who achieved the reduced goal blood pressure had a significant reduction in their risk of stroke. The risk was almost 30% lower for those who achieved a diastolic blood pressure of less than 80 mm Hg compared for those who only achieved a diastolic blood pressure of less than 90 mm Hg. Furthermore, compared to the other target groups, cardiovascular mortality was significantly reduced in this group (diastolic blood pressure less than 80 mm Hg). Furthermore, the risk for all is decreased non-significantly in the group with more stringent blood pressure control [9][24].

Active antihypertensive medication treatment decreased overall mortality by 55%, mortality from cardiovascular causes by 76%, all cardiovascular events by 69%, fatal and nonfatal stroke by 73%, and all cardiac events by 63% after a two-year follow-up in the Syst-Eur trial, which included 492 patients (10.5%) with DM [9][25]. In comparison to patients receiving a placebo, DM patients who were randomly assigned to active therapy with antihypertensive drugs in the SHEP study showed reduced rates of stroke, nonfatal Myocardial Infraction(MI), fatal coronary heart disease (CHD), major coronary events, and all-cause mortality [9][26].

In individuals with DM, intensive antihypertensive medication (mean blood pressure 133/78 mmHg) significantly reduced all-cause stroke compared to moderate antihypertensive therapy (mean blood pressure 139/86 mmHg), according to the Appropriate Blood Pressure Control in Diabetes (ABCD) trial [9][27]. This is significant because patients who have both DM and HTN have a higher risk of stroke, both fatal and non-fatal. In conclusion, current evidence demonstrates the essential impact that blood pressure has on CVD in DM, which strongly supports the control of HTN in the setting of DM, even though exact objectives are still debatable [9].

INTERCONNECTION BETWEEN HTN AND ASTHMA

While the impact of blood pressure management on asthma is still mostly unknown, lowering systolic blood pressure to less than 130 mm Hg lowers the chance of dying from CVD [11–14]. Type 2 high inflammation and type 2 low inflammation are the two primary endotypes of asthma that are officially recognised as a condition. These subtypes can be roughly classified according to their major underlying mechanism, which is mostly dictated by the cytokines and T cells or innate lymphocytes involved. Clinical characteristics, pathological findings, and biomarkers (chemokines) can be used to further classify each endotype into a number of phenotypes. Although estimates of the prevalence of type 2 high- and type 2 low-inflammation endotypes differ due to the lack of consistent criteria for categorising types of asthma, each endotype seems to account for roughly half of the asthmatic population [29].

Some people with asthma may be more susceptible to HTN due to a combination of age, neurological system failure, and genetic factors. The risk of obesity, metabolic syndrome, and the resulting increase in systemic inflammation are all influenced by diet and lifestyle choices. Adipose tissue's production of interleukin-6 plays a role in vascular and airway disorders. Another frequent element that exacerbates illness is stress. Both improper RAAS activation and changes in the microbiota are associated with the development of HTN and more severe illness in individuals who consume a high-salt diet. Pollutants, bacteria, viruses, and other environmental elements can all operate as innate immune response stimuli, triggering type 1 or type 17 pro-inflammatory reactions.

Through the activation of cytokine cascades via protease-activating receptors, exposure to allergens such dust mites may contribute to inflammation that is distinct from adaptive type 2 high-inflammation responses. When hypertensive individuals with asthma have innate and adaptive immune profiles, they primarily exhibit a type 2 low-inflammation endotype. This endotype has a role in structural remodelling, mucous secretion, smooth-muscle hypertrophy and hyperplasia, and airway hyperresponsiveness in asthma. Vascular tone and blood pressure rise as a result of the inflammatory environment in asthmatic individuals with HTN [29].

There is no mechanistic connection between HTN and type 2 elevated asthma (Panel A). Furthermore, type 2 cytokines like interleukin-4 and interleukin-13 encourage macrophages to adopt the M2 phenotype rather than the M1 phenotype linked to HTN. There are several molecular connections between type 2 low asthma and the inflammation that causes HTN (Panel B). Both the manifestation and severity of asthma and HTN may be influenced by immune responses that are biassed towards types 1 and 17 [29]. While interleukin-6 helps to down-regulate regulatory T cells (Tregs), which prevent inflammation in both HTN and asthma, interferon-γ also stimulates M1 macrophages, which both activate adipocytes and directly cause HTN.

ILC2 and ILC3 stand for Th1, Th2, and Th17 type 2, type 3, and type 17 helper cells; PGD2 prostaglandin D2; ROS (reactive oxygen species); and TSLP (thymic stromal lymphopoietin). These cytokines work together to promote fibrinogenesis, smooth-muscle activation, and inflammation—all of which are essential components of cardiovascular and respiratory disorders. As a result, individuals with both asthma and HTN seem to make up a patient subgroup with a disease that is challenging to treat and that is more likely to cause end-organ damage [29].

Recent Advances in HTN Management

Despite a constant age-standardized prevalence globally, a recent study found that the number of participants aged 30–79 years with a prior diagnosis of HTN doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019 [30]. About 70% of the global burden of disease and mortality is thought to be explained by a systolic blood pressure of 140 mmHg or higher. The percentage of treated hypertensive people with normal blood pressure (also known as "controlled HTN") is still quite low globally, despite this remarkable increase.

According to estimates, this percentage is close to 23% for women and 18% for males [30, 31, 32].

Notably, significant differences still exist globally even though the majority of developed and wealthy nations have made progress in the diagnosis, management, and control of HTN. In fact, almost two-thirds of HTN sufferers reside in low-income nations. In a number of sub-Saharan African and Oceanian nations, there has been little progress in raising awareness, treating, or controlling HTN during the last 20 years [30]. A second factor to take into account is that, in spite of the enormous volume of observational research and randomised controlled trials that have been carried out over the previous forty years, there have been very few novel investigations conducted in recent years. Research on novel HTN medications and therapeutic targets is significantly slowing down, according to a thorough study by Dzau [30][33].

Chronotheraphy

The overwhelming predictive impact of evening blood pressure has been proven beyond a reasonable question by numerous investigations carried out at independent centres [30][34]. Accordingly, it has been suggested that taking antihypertensive medications before sleep rather than in the morning may be better for regulating blood pressure, preventing or reversing organ damage, and lowering the risk of CVD. Evening administration may, in fact, lower the incidence of significant cardiovascular events linked to HTN, according to data from a Spanish study group [30][35][36]. Antihypertensive medication delivery in the morning and the evening has not been shown to differ in terms of blood pressure control in other research [30][37][38]. To provide a definitive response to this topic, a massive randomised investigation called the TIME study is currently in progress [30][39 For the time being, it seems appropriate to recommend that some patients with severe or resistant HTN, as well as those with exceptionally high blood pressure at night, take antihypertensive medications in the morning and the evening. Antihypertensive medications with a long half-life that can last the full twenty-four hours should be preferred. For instance, in patients without severe renal failure, chlorthalidone seems to be the top choice when selecting a diuretic. [30], [40], and [41]. Patients with uncontrolled HTN and renal failure (glomerular filtration rate between 15 and 29 mL/min/1.73 m2 of body surface area) were randomly assigned to receive chlorthalidone or a placebo in a recent trial. The randomisation process was stratified by the patients' history of using loop diuretics.Following a 12-week course of treatment, the chlorthalidone group's average 24-hour systolic blood pressure was 10.5 mmHg lower than that of the placebo group ($p < 0.001$) [30][42].

MORE FREQUENT USE OF MINERAL-CORTICOID RECEPTOR ANTAGONISTS

For 12 weeks, 335 patients with home systolic blood pressure (BP) > 130 mmHg despite maximal therapy were randomly assigned to receive spironolactone (25–50 mg), bisoprolol (5–10 mg), doxazosin modified release (4–8 mg), and placebo in addition to their baseline blood pressure medications. This was done in a double-blind, placebo-controlled, within-patient trial called PATHWAY-2. More than placebo (–8.7 mm Hg), doxazosin (−4.03 mm Hg), and bisoprolol (−4.48 mm Hg), spirolactone decreased home systolic blood pressure [30][43]. Therefore, spironolactone was the most effective antihypertensive drug, independent of baseline plasma renin distribution, even though the aldosterone-renin ratio and plasma renin activity predicted its BP-lowering impact [30][44]. In contrast to the comparable medications, spirolactone decreased the amount of thoracic fluid [30][44].
Notably, amiloride does not cause gynaecomastia because it does not have the antiandrogen effect of spironolactone. Since eplerenone seems to have a superior safety profile than spironolactone, it could be used in its place [30][45][46]. However, hyperkalaemia is a side effect that should be properly watched in people taking mineral-corticoid receptor antagonists. Anti-aldosterone drugs are currently recommended for patients with resistant HTN [30]. It's safe to predict that more people will utilise these drugs in the future.

ENDOTHELIN RECEPTOR ANTAGONISTS

Endothelin has a potent vasoconstrictor effect and plays a role in the pathophysiology of HTN by controlling blood pressure and vascular tone. It results in increased aldosterone synthesis and secretion, fibrosis, endothelial dysfunction, neurohormonal and sympathetic activation, and hypertensive end-organ damage [30][47][48]. Moreover, endothelin-1 (ET-1), the biologically dominant member of the endothelin peptide family, is a peptide generated from endothelial cells that has a wide range of physiological and developmental roles, including nociception and embryogenesis. More precisely, the development of the particular neural crest cell population and its derivatives is regulated by the endothelin system [30][49]. Some studies have assessed the antihypertensive effectiveness and acceptability of medications that can block the endothelin-A and endothelin-B receptors, based on data that endothelin is a highly strong endogenous vasoconstrictor. The tolerability of endothelin receptor antagonists is still an issue, though, and the results are somewhat poor. The use of these medications in clinical practice may be restricted due to their potential side effects, which include headaches, flushing, and fluid retention. [30][50]. Due to safety concerns, the development of endothelin-A blockers and darusentan was halted [30].

NEPRILYSIN COMBINED WITH RENIN-ANGIOTENSIN SYSTEM INHIBITION

Neprilysin is a zinc endopeptidase that inactivates bradykinin as well as cardiac natriuretic peptides, causing vasodilatation and natriuresis as a result of these agents' longer-acting effects. Neprilysin was created in combination with medications that block the renin-angiotensin-aldosterone pathway rather than as a monotherapy for clinical usage [30][51]. Due to the occurrence of severe angioedema, the development of omepatrilat, the first-in-class combination of naprilysin and an angiotensin-converting enzyme inhibitor, was discontinued [30][52]. On the other hand, LCZ696, a more contemporary drug that combines neprilysin with valsartan, an angiotensin II receptor blocker, in one molecule, has been shown to be both efficacious and well-tolerated in treating HTN and heart failure [30].

ANGIOTENSIN-2 RECEPTOR AGONISTS

By activating the angiotensin 1 and angiotensin 2 receptors, respectively, angiotensin II causes vasoconstriction and vasodilatation. Angiotensin 2 receptor stimulation reduces blood pressure, causes vasodilatation, natriuresis, and prevents fibrosis in both clinical and experimental contexts. As a result, angiotensin II receptor agonists are being studied for their effectiveness and safety and show intriguing antihypertensive potential [30].

TREATMENT OF HTN ASSOCIATEDWITH DIABETES [29]

HTN was classified as either stage 1 (130–139/80–89 mm Hg) or stage 2 (>140/>90 mm Hg) in the 2017 report of the American College of Cardiology–American HeartAssociation Task Force on clinical practice guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults. For individuals with or at high risk for CVD at stage 1 and for all patients at stage 2, pharmacotherapy was advised. Notably, the 2017 guidelines lowered the threshold for a diagnosis of HTN, which has caused significant debate because it increased the proportion of adults in the US with a diagnosis of HTN from 32% to 46%.

Beta-Blockers

Because of worries about unopposed bronchoconstrictive signals and the therapeutic response to β2-agonists, patients with asthma should be introduced to beta-blockers with some caution. Additionally, although there may be special justifications for patients with congestive heart failure who have arrhythmias or have experienced myocardial infarction, beta-blockers are not often advised as monotherapy for the treatment of HTN in people with the majority of diseases.

Angiotensin-Converting–Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are helpful in people with asthma and HTN; they are not contraindicated, as is the case with patients with HTN in general. However, because exposed patients may acquire an ACE inhibitor-related cough, clinical misunderstanding regarding asthma control may occur during treatment. Depending on factors including ethnicity, genotype, the existence of underlying CVD, evaluation methodology, and the particular ACE inhibitor administered, the incidence of this adverse effect might vary from 2.8 to 40%. In certain hypertensive patients, ACE inhibitors have also been linked to an increase in the severity of asthma.

Angiotensin-Receptor Blockers

Patients with asthma who also have HTN may benefit from using angiotensin-receptor blockers (ARBs), which work on the renin-angiotensin system. It was discovered that during exacerbations, people with severe asthma had higher levels of circulating renin and angiotensin II than those who did not. In patients with mild asthma, experimental angiotensin II infusion also resulted in a drop in FEV1 and an increase in coughing or chest tightness feelings. Bronchial hyperresponsiveness has been slightly reduced as a result of angiotensin II type 1 receptor inhibition. It seems that ARBs target mechanisms that would treat asthma and HTN.

Calcium-Channel Blockers

In patients with asthma who also have HTN, there may be advantages to using calcium-channel blockers. This class of drugs causes modest bronchodilation, reduces smooth-muscle contraction, and eases bronchoconstriction brought on by a number of stimuli, such as exercise, histamine, cold air, and certain antigens. However, there is no evidence that calcium-channel blockers improve asthma outcomes in clinical settings. However, calcium-channel blockers are a preferred treatment for those with asthma who also have HTN because of their physiological profile and effectiveness.

Thiazides

Low-dose thiazides are frequently recommended to treat HTN, either by themselves or in conjunction with other medications such calcium-channel blockers. High dosages of β2 agonists in asthma can cause hypokalaemia, which seems to be more severe in patients on diuretics and is hence susceptible to the arrhythmogenic potential that results. Adding a glucocorticoid or theophylline to a patient with asthma and HTN who is on diuretics and a β2 agonist may increase the risk of hypokalaemia.

TREATMENT OF HTN ASSOCIATED WITH ASTHMA [53]

Many randomised controlled trials (RCTs) and meta-analyses using diuretics, α-blockers, calcium channel blockers (CCBs), betaadrenergic antagonists (ß-blockers), and RAAS blockade with angiotensin converting enzyme inhibitors (ACEI) and angiotenin receptor blockers (ARBs) found that treating HTN in the elderly and very elderly (>80 years) patient population was linked to significant decreases in CV events and mortality. Each 10-mmHg drop in SBP in hypertensive diabetics was linked to a significant decrease in the risk of any diabetes-related complications, diabetes-related deaths, myocardial infarction (MI), and microvascular complications, according to the UKPDS (UK Prospective Diabetes Study) study. However, with a mean age of 56, the UKPDS study population was comparatively younger.

Diuretics

The mainstay of treatment for HTN has been diuretic pharmaceuticals, particularly thiazide diuretics. Studies using chlorthalidone provide a large portion of the information now available on the safety and effectiveness of thiazide diuretics in elderly HTN patients. Numerous studies have demonstrated that thiazide diuretics are more clinically effective than placebo and other widely used antihypertensive drugs like α-blockers, CCBs, ß-blockers, and ACEIs in lowering CV morbidity and mortality in older hypertensives. The Systolic HTN in the Elderly Program (SHEP) trial shows that chlorthalidone medication improves cardiovascular outcomes, including a lower risk of coronary heart disease (CHD), MI, stroke, HF, and mortality when compared to a placebo. In the SHEP, the average age at randomisation was 72 years old. Chlorthalidone was just as effective as amlodipine and lisinopril in lowering the number of fatal CHD events and non-fatal MI events in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) study [43]. Chlorthalidone medication dramatically decreased aggregate CV and stroke events in comparison to lisinopril, HF events in comparison to

amlodipine, and SBP in comparison to both amlodipine and lisinopril [43]. About 36% of patients had DM, and the mean patient age was 67 years, with 58% of patients being over 65 [42]. The ALLHAT study's findings held true for both age and diabetes status [43]. These findings are predicated on the use of thiazide diuretics as a first-line treatment for HTN.

ß-blockers

ß-blockers have long been used to treat a number of cardiovascular conditions, most notably HTN. Popular ß-blockers are a broad class of medications with a range of pharmacologies and modes of action, including vasodilatory, cardio-selective, and conventional non-selective ß-blockers. Traditional ß-blockers lower blood pressure through their negative ionotropic and chronotropic effects on the heart, and vasodilatory ß-blockers have additional peripheral vasodilatory properties from α-receptor blockade, though the precise antihypertensive mechanisms of these medications are still unclear. By inhibiting the kidney's ß-1-receptor, ß-blockers also lower plasma renin production, which adds to its antihypertensive properties. Numerous RCTs and meta-analyses assessed the usefulness of this class of drugs in lowering CV events both on their own and in conjunction with other antihypertensives. The authors of a recent Cochrane database meta-analysis of 13 RCTs from the 1970s to the 2000s came to the conclusion that starting ß-blockers to treat HTN results in modest reductions in CV disease and little to no mortality effects, and that these effects are not as good as those of other antihypertensive medications. In four RCTs, ßblockers were compared to a placebo; in five RCTs, diuretics; in four RCTS, CCBs; and in three RCTs, RAAS inhibitors. The scientists also observed that while there was little to no difference with placebo, diuretics, or CCBs, those on ßblockers were more likely than those on RAAS inhibitors to stop treatment because of side effects.

Calcium-Channel Blockers

CCBs are a diverse class of medications with a range of pharmacological characteristics. They dilate peripheral and coronary arteries by lowering calcium input into arterial smooth muscle cells. The dihydropyridine CCBs, such as amlodipine and nifedipine, are more effective at reducing blood pressure and causing vascular relaxation because they selectively block calcium channels in the vascular smooth muscle. Early data suggested that the dihydropyridine CCB nitrendipine, as opposed to a placebo, decreased the incidence of stroke, severe cardiovascular events, and cognitive impairments in the Syst-Eur (systolic HTN in Europe) and Syst-China (systolic HTN in China) trials. The elderly patients who were enrolled in these trials ranged in age from 67 to 70. Several RCTs assessed their relative effectiveness in lowering hypertensive consequences. In older patients with combined systolic/diastolic HTN, the dihydropyridine CCB (felodipine or isradipine) was compared with an ACEI or a diuretic/ß-blocker in the STOP2-HTN (Swedish Trial in Old Patients with HTN) trial. The results showed a comparable decrease in the incidence of combined CV events. Diltiazem was found to be just as beneficial as diuretics, ß-blockers, or both in preventing the combined primary end point of all stroke, MI, and other CV mortality in the Nordic Diltiazem (NORDIL) research. In older individuals with HTN and CHD, the International VerapamilTrandolapril Study (INVEST) showed that the combination of verapamil and an ACEI was just as effective in lowering CV events and regulating blood pressure as an atenolol-thiazide combination.

RAAS inhibitors

In the end, ACEI and ARBs work by blocking the effects of the potent vasoconstrictor angiotensin II, which lowers blood pressure both systemically and in peripheral arteries. While ACEIs have been shown to be beneficial in older persons with HTN in a number of RCTs, older hypertensives have had less experience with ARBs. Patients with DM were examined for ACEIs and ARBs more often than for other antihypertensive medications. According to the ALLHAT research, ACEIs are just as effective at lowering CV events as CCBs and diuretics. It should be mentioned that in the ALLHAT, chlorthalidone outperformed the ACEI lisinopril in preventing angina, HF episodes, coronary revascularisation, and stroke (in blacks). In hypertensive diabetic patients, the ACEI fosinopril had a considerably reduced risk of the combined outcome of acute MI, stroke, or hospitalised angina than those receiving amlodipine, according to the FACET (Fosinopril vs. Amlodipine Cardiovascular Events Randomised Trial). In a large sample of patients with high-risk vascular disease alone, ramipril medication was linked to significant decreases in risks of MI, stroke, and CV death as compared to placebo in the seminal HOPE (Heart Outcomes Prevention Evaluation) research. Just 47% of the individuals in this trial had HTN. The HOPE study's Micro-HOPE substudy found that ramipril significantly decreased the combined primary outcome of MI, stroke, or CV mortality in older patients with DM (mean age 65 years, HTN 56%).

According to data from RCTs and meta-analyses (ALLHAT, HOPE, LIFE, VALUE, and others), both ACEIs and ARBs were linked to lower incidence of new-onset DM. According to a network meta-analysis, the odds ratio for new-onset diabetes as compared to diuretic medication is 0.62 (0.51–0.77) for ARBs, 0.67 (0.57–0.79) for ACEIs, 0.75 (0.63–0.89) for placebo, 0.79 (0.67–0.92) for CBBs, and 0.93 (0.78–1.11) for β-blockers. The increased delivery of insulin and glucose to skeletal muscle and fat due to RAAS inhibition, effects on glucose transport, a reduction in the potassium-lowering effect of insulin and a decrease in incident hypokalaemia, and peroxisome proliferator-activated receptor-gamma agonism were the hypothesised mechanisms to account for these findings.

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